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A.M.A. JOURNAL OF

DISEASES OF CHILDREN

Editorial

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J. A. James and J. S. Robertson

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F. Thomas Mitchell

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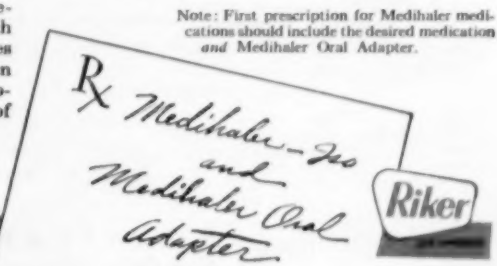

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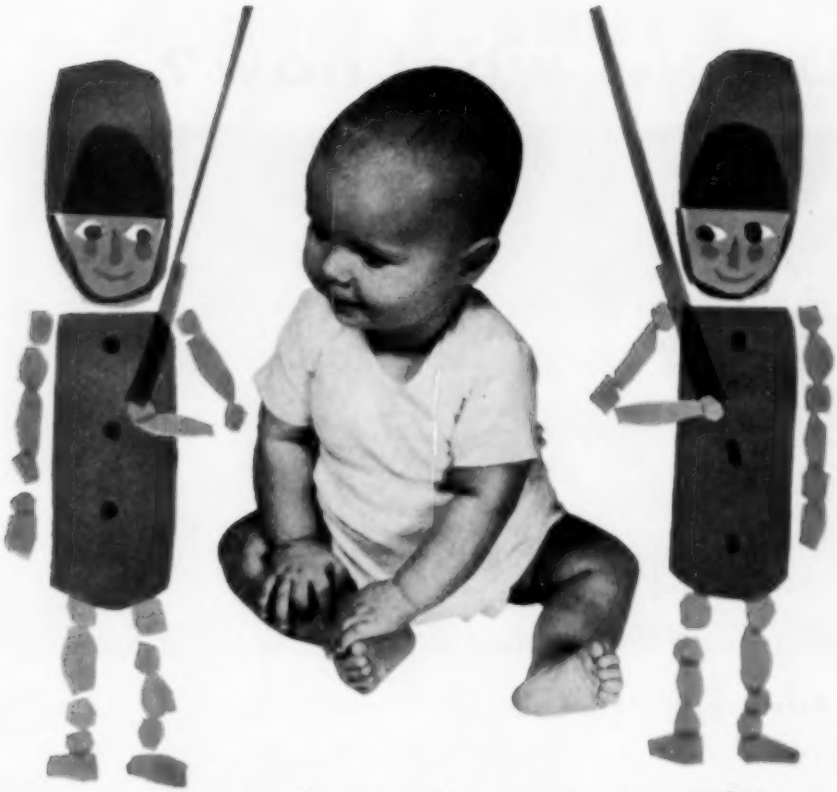

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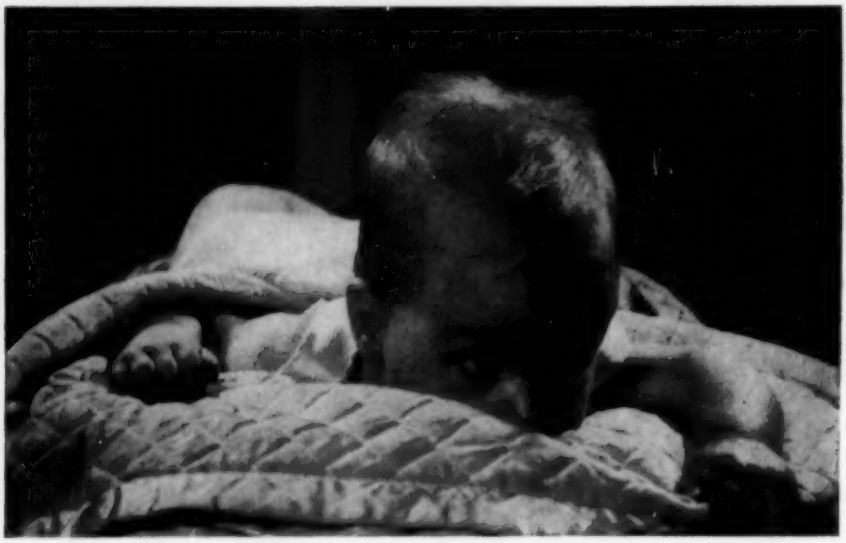

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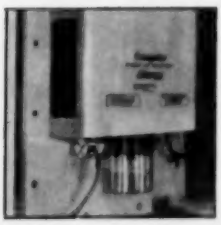

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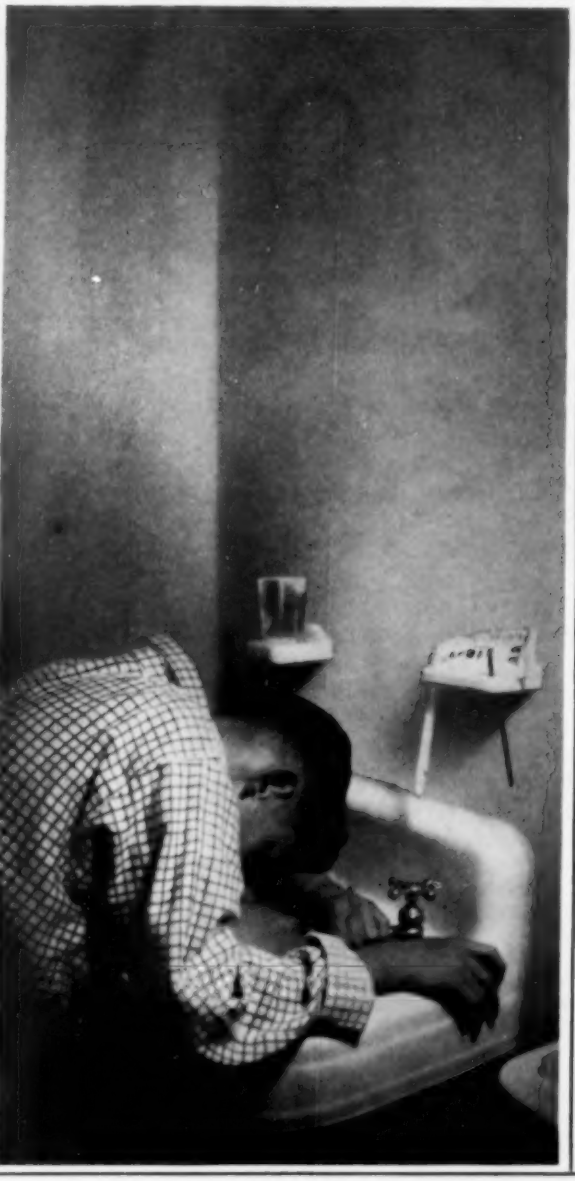

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Estimation of Exchangeable Water and Potassium by Radioisotope Dilution in Children

J. A. JAMES, M.R.C.P., and J. S. ROBERTSON, M.D., Ph.D., Upton, N. Y.

Most measurements of the total body water in man using dilution techniques have been made using antipyrine or deuterium oxide (D_2O) as tracers. In adult subjects, Schloerb and co-workers, using D_2O, obtained mean values of 61.8% and 51.9% of the body weight in male and female subjects, respectively.[1] Slightly lower values have been reported using antipyrine.[2,3] Body-water percentage appears to decrease with advancing years, apparently due to increase of body fat.[6] The earlier literature on body-water measurements by desiccation and other methods has been reviewed by Levitt and Gaudino[7] and by Pace and associates.[8]

In children, Friis-Hansen and co-workers[4] determined that body water constituted from 53% to 63% of body weight in "hospital normal" children over 6 months of age, regardless of sex. Higher values were obtained in young infants.

Apart from the patient studied by Pace[8] and the series of Pinson and Anderson[5] and Prentice and co-workers[6] in adults, few measurements using tritiated water (HTO) have been reported, possibly because the methods available for counting tritium have been tedious and difficult. The recent introduction of liquid-phase scintillation counting, however, has greatly simplified the counting of low-energy β-particles, and tritium water samples can now be counted rapidly and with accuracy.

The purpose of the present investigation was (a) to study the kinetics of mixing, volume of distribution, and biological decay of HTO in children, (b) to compare the values for total body water obtained, using a simple technique to prepare HTO samples, with those using another method (antipyrine), and (c) to relate body water and exchangeable potassium content.

Procedure and Methods

The children studied were hospitalized at, or had recently been discharged from, the Nephrotic Unit of the Brookhaven National Laboratory Medical Center. All had proteinuria, but, with the exception of Case 9, who was approximately 1 kg. over her non-edematous weight, none had edema, and the plasma proteins were near normal. All were ambulant but did not engage in strenuous activities before the studies. Studies were started about two hours after breakfast, and from this time until all samples for body-water determination had been obtained (four hours) oral fluids were restricted to 60 ml. After the drawing of a control blood sample, a slow (0.3 to 0.5 ml/minute) intravenous infusion of normal saline was started. With the use of a fine (No. 24) needle to prevent leakage from the puncture site, 3 μc/kg.

Submitted for publication July 23, 1956; accepted Aug. 31.

Medical Department, Brookhaven National Laboratory.

This work was supported by the Atomic Energy Commission.

Dr. James' present address is Department of Pediatrics, The University of Texas, Southwestern Medical School, Dallas 19, Texas.

of K^{42}, 75 μc/kg. of HTO,* and 400 mg. of antipyrine† in 10 ml. were then injected‡ through the intravenous tubing close to the infusion needle. A second 10 ml. of the mixture was expelled with the same syringe into a volumetric flask for dilution as a standard for all three substances. Timed blood samples were taken without stasis through a side-arm close to the needle, the syringe being "rinsed" once or twice with blood to minimize contamination with saline. The infusion was removed after one hour, the total amount of saline infused not exceeding 50 cc. Subsequent venous samples were taken at 2, 3, and 4 hours for body-water determinations or at intervals up to 14 days for study of biological decay of HTO. Plasma was separated promptly and stored under refrigeration in tightly stoppered tubes sealed with Parafilm. Urine samples were similarly stored after measurement of volume.

Antipyrine was determined by the method of Brodie and co-workers.[9] Exchangeable potassium was determined by the principle of Corsa and associates.[10] An Amberlite IR-120 column was used to concentrate urine potassium,[11] and potassium concentrations were estimated using a Baird internal standard flame photometer. A well-type crystal scintillation counter was used to count the K^{42}. Plasma and urine water for tritium estimation was obtained by the method of Ussing and Wernstedt,[12] samples being evaporated in 60×15 mm. Petri dishes sealed with Scotch No. 33 electrical tape and the water collected on the solid-CO_2-cooled lid. Standards were subjected to the same procedure. For counting, 0.1 ml. sample water, 3 ml. absolute alcohol, and 12 ml. of a 3% solution of the phosphor PBD (2-phenyl-5-[4-biphenylyl]-1,3,4-oxadiazole) in xylene were pipetted into vials and counted in a liquid scintillation counter.§ Tritium counting was performed five to seven days after the study, at which time the K^{42} had decayed to 0.001 or less of its initial activity.

The mean of the HTO counts at one, two, three, and four hours was used as the equilibrium value for calculating total body water. The concentration of antipyrine at zero time was estimated by extrapolation of the best straight line obtained from the four points by the method of least squares. In four instances plasma water was estimated by a desiccation method. In the remainder a correction factor of $1/_{0.93}$ was used to convert concentrations in plasma to concentrations in water. As plasma proteins were near normal in these children, it is not thought that this assumption introduced a significant error.

Exchangeable potassium was calculated from the specific activities of three urine samples taken between 24 and 32 hours after injection of K^{42}. By this time probably 95% of the body potassium has exchanged with K^{42}.[11]

Results

Summarized data on total body water and exchangeable potassium are given in Table 1 and turnover data in Table 2. Figures 1 and 2 show curves of equilibration and biological decay in individual children.

Total Body Water (TBW) (Table 1).—In this small series, TBW measured by HTO varied from 49.7% to 59.1% of the body weight with a mean of 55.1%±3.1%. The values obtained with antipyrine were slightly higher, with a mean of 56.3%±5.4%. The coefficients of variation were

* The irradiation from K^{42} is about 140 millirad and that from tritium about 160 millirad when these doses are administered. These add up to the integrated permissible radiation dose for eight days. (One rad equals 100 ergs of ionizing radiation per gram of tissue.)

† Supplied through the courtesy of the Eli Lilly Company, Indianapolis.

‡ In early studies the substances were injected separately. The same technique for preparation of standards was used.

§ Packard Instrument Co., Model 314, Tri-Carb Liquid Scintillation Spectrometer.

TABLE 1.—*Total Body Water and Exchangeable Potassium*

Case	Age, Yr.	Weight, Kg.	Surface Area, M^2.	Total Body Water			Exchangeable Potassium	
				HTO	Antipyrine	% Body Weight (HTO)	mM	mM/Kg.
1 (1)	4 5/12	23.1	0.77	11.47	11.32	49.7	....	....
2	3 9/12	17.3	0.66	10.20	10.11	58.9	838	48.4
3	2 ½	14.2	0.59	7.58	7.89	53.4	605	42.6
4	7 ½	23.6	0.87	12.26	12.66	51.9	1124	47.6
5	5	20.6	0.79	12.17	13.88	59.1	852	41.4
6	8 ½	29.4	1.03	15.23	15.26	51.8	1297	44.1
7	2 ½	15.9	0.62	9.01	9.70	56.7	....	....
8 (2)	4 ½	23.9	0.79	13.49	13.25	56.4	983	41.1
9	8 ½	27.3	0.95	15.76	14.89	57.7	1183	43.3
						55.1±3.1		44.1±2.9

6.3% and 9.6%, respectively, reflecting the difficulty of obtaining wholly satisfactory antipyrine curves. Expressed in terms of surface area, tritium and antipyrine gave total body water volumes of 15.1±1.3 and 15.4±1.3 liters/sq. meter, respectively.

In one subject who was studied on two occasions two months apart (cases 1 and 8), an apparent change in body water occurred which was not reflected in an equal change in body weight. Close agreement between the antipyrine and tritium values was observed on both occasions.

Exchangeable Potassium (E_K) (Table 1).—In the seven patients in whom it was measured, E_K ranged from 41.1 to 48.4 mM/kg. with a mean of 44.1±2.9 mM/kg.

TABLE 2.—*Rate of Turnover of Body Water*

Case	Surface Area (M^2)	Half-Time (Days)	Turnover Rate* (Per Cent per Day)
3	0.59	4.17	16.6
7	0.62	4.58	15.2
2	0.66	5.29	13.1
1 (1)	0.77	5.17	13.4
5	0.79	5.58	12.4
4	0.87	3.71	18.7
9	0.95	7.96	8.7
6	1.03	6.29	11.0
Mean	....	5.3	13.6
Adults (1)	....	7.3-13 (9.3)	5.3-9.5 (7.7)

* Turnover rate $\% = \frac{0.69315}{\text{half-time}} \times 100\%$.

This corresponds to approximately 80 mM/L. of total body water, or, assuming that intracellular fluid constitutes two-thirds of the total body water, to approximately 120 mM/L. of intracellular water.

Characteristics of the Early Curve (Fig. 1).—In all instances tritium water apparently equilibrated with the systemic body water within 30 to 40 minutes. Distribution occurs with great rapidity. For example, in Case 3 (Fig. 1) the space defined at two minutes was 50% of the equilibrium value and equilibration was virtually complete in 10 minutes. Because mixing in the plasma and distribution to other tissues are occurring simultaneously, it is not possible even with the use of arterial samples to determine meaningful characteristics of the early part of the plasma tritium curve.

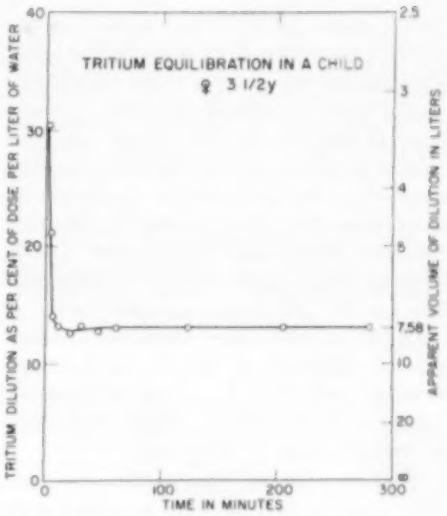

Figure 1

Biological Decay (Table 2, Fig. 2.) In eight children blood samples for HTO determination were taken at intervals up to 9 to 14 days from the time of study. In all instances, decay was apparently defined by a single exponential. The half-time varied from 3.7 to 8.0 days corresponding to a turnover rate of 18.7% to 8.7% of the body water per day. With the exception of Patient 4 the half-time was roughly proportional to the size of the child. In three children in whom continuous urine collections were made, the urine specific activities at the time of blood sampling closely paralleled plasma specific activities (Fig. 2).

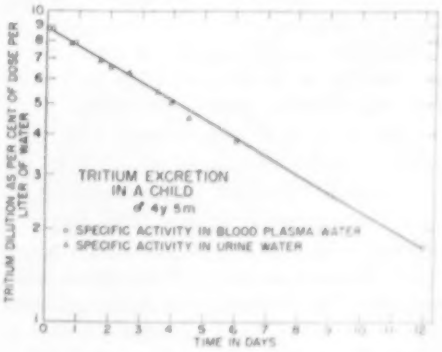

Figure 2

Comment

Both D_2O and HTO fulfill the theoretical requirements for a water tracer more adequately than does antipyrine. The evidence does not suggest that the greater mass of D or T gives rise to any significant isotope effect when they are used for this purpose.[6] In addition, these isotopes mix readily with abnormal fluid collections[3,6] and permit study of urine specific activities,[13] distribution kinetics, and turnover rates,[1] none of which is possible with antipyrine. About 2% of the tracer is believed to enter the metabolic pool.[12] If this is true the apparent volume of distribution is slightly larger than the actual volume of body water.

The present study suggests that total body water may be satisfactorily measured with HTO. The technique used is simpler than that required for D_2O determination, and compares favorably with the antipyrine method for rapidity.

In the present small series, HTO and antipyrine defined approximately the same volumes of body water. No conclusions can be drawn regarding the inconsistent differences observed between the two methods, although it is possible that they may have been due to technical difficulties experienced with the antipyrine method. In larger series, the D_2O space has usually measured from 2% to 4% larger than the antipyrine space.[2,3]

In the present study total body water measured with HTO ranged from 50% to 59% of the body weight. This closely approximates the 53% to 63% obtained by Friis-Hansen and co-workers using D_2O, in 12 children over 6 months of age. Since the children in the present study were convalescent from a prolonged illness, it is possible that their tissues may have contained a higher proportion of fat than the more strictly "normal" children studied by Friis-Hansen and associates. This factor is believed to account for the lower body water values obtained in older and less active adult patients.[6] The exchangeable potassium content of normal children has been reported as 37 to 47 mM/kg.[14] The values obtained in the present series (41 to 48 mM/kg.) are comparable.

The disappearance curves of tritium water indicated that these children who were on ad lib. fluid intake and somewhat restricted activity exhibited a body water turnover rate approximately twice that of the adult.[1] These data are in accordance with the calculations of Gamble[15] showing that young children are less able to tolerate fluid depletion than adults because of their higher obligatory water losses relative to body content, and in fact have a theoretical survival margin only half that of the adult.[15] As demonstrated by Pinson and Anderson,[5] the rate of body water turnover can be greatly altered by changing the fluid intake.

From the clinical standpoint, it might appear that a simple method for measuring total body water would be of value in assessing the severity and the fluid requirements in states of dehydration. However, it appears that the range of normal values is so wide that a child could be severely dehydrated and still have a body water value within the normal range, and, secondly, serial determinations in our hands (the patient in Cases 1 and 8) and in the hands of others[3,16] indicate apparent variation in body water content inconsistent with changes in body weight or hydration. The reason for this is obscure. In the patient in Cases 1 and 8 the close correlation between antipyrine and HTO values in both instances makes errors in determination an unlikely cause, and it is not believed that so large an error could have occurred in the administration of the test materials. A likely, but in this instance unproved, possibility is that, during the interval, body fat was lost and body water increased so that little change in weight occurred. Another possibility is that variations in the exchangeability of water may occur from time to time. These results support the contention of Friis-Hansen[4] that although body water can be measured with reasonable accuracy, the determinations will not be of clinical use until these variations are explained and a

simple method is available for the measurement of total body fat. The values, however, are of physiological interest, offering an approach to the study of the factors involved in the distribution of water and electrolytes in the body.

Very recently, the data of Corsa and associates on exchangeable potassium in normal children[14] have been published *in extenso* together with measurements of total body water and sodium.[17] The results are in accordance with the present data, suggesting that these children, despite prolonged illness, represented a normal group as far as water and potassium distribution are concerned.

Summary

Total body water was measured by tritium oxide and antipyrine dilution in nine convalescent children. The tritium samples were prepared for counting by a simple distillation method and counted in a liquid scintillation counter. The processes of equilibration and biological decay of tritium water were also studied.

Equilibration was complete within 30 to 40 minutes in all instances. Tritium water and antipyrine defined similar volumes of body water (55% and 56% of body weight), which were close to values previously reported. The turnover rate of body water in these children averaged 13.6% per day, approximately twice that observed in the adult.

Measurements of whole body exchangeable potassium were also made in seven children and varied from 41 to 47 mM/kg. or approximately 79 mM/L. body water.

The present data tend to confirm that total body water measurements are of little clinical value at the present time due to the wide range of normal values and also to unexplained variations in serial determinations.

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Editorial

The Editorial Board of the A. M. A. JOURNAL OF DISEASES OF CHILDREN is happy to announce the addition of the following men as Associate Editors:

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The complexity of modern medical research and practice is such that more specialized knowledge of certain fields is demanded in order to present accurately reviewed contributions. With this goal in mind, the A. M. A. JOURNAL OF DISEASES OF CHILDREN has been most fortunate in gaining the help of this distinguished group of investigators and clinicians.

Chairman's Address

F. THOMAS MITCHELL, M.D., Memphis

Last year this Section saw fit to elect me Chairman of this year's meeting. I thank you for this, one of the highest honors I have received. Great moments in one's life are marked by profound emotion. My emotions are in this moment deeply stirred with appreciation; however, I feel many men in this Section more fully deserve this office, any one of whom is better qualified to fill this position.

On thinking of how little I can contribute to this meeting I am much embarrassed to occupy this Chair which through the years has been so ably filled by many of the really great men in pediatrics. Since the Secretary has prepared the program and made all the arrangements, I have no doubt that this year's program will be executed in the usual good form and with the usual exhibition of knowledge of the material presented.

While certain aspects of pediatrics have not changed, many new facts and practices have been introduced as pediatric knowledge has grown. Since this Section was organized in 1880 with Dr. Abraham Jacobi its first chairman, the programs of this Section have presented all phases of pediatrics at all times, and explored new fields as they appeared. The real contribution the Section on Pediatrics has made through the many years speaks for the knowledge, zeal, expertness, and productivity of the men who have contributed to these programs.

In the preparation of this presentation my memories and my thoughts were stimulated by a deep love for pediatrics, a sincere and high respect for those men who made pediatrics what it is, and a lively interest in the work and ambitions of this Section which endeavors to improve all phases of child care. My aim is to stimulate interest in the present opportunities of the Section.

Today the human mind visualizes life on an ever expanding scale. As the range of an individual's and an organization's knowledge and obligation grows, the range of loyalty and support likewise broadens. This is as true in medicine as it is in any other field of human endeavor. It is also true of the Section whose business it is to study the newborn, infant, and child in health and in all the variabilities from normal which are called disease. This Section has obligations to American practitioners which are as great today as at any previous time. It is our business not only to present all phases of pediatrics to these annual assemblies by papers and exhibits but also to find opportunities in other directions which might prove valuable to American medicine.

These meetings offer the country's best opportunity for pediatricians and men in other specialties and in general practice to discuss the needs of each group and together decide mutual problems. The Section of Pediatrics, therefore, should endeavor to attract men in all branches of medicine to its meetings and to interest them in its activities as well. In this way the Section could fulfill its obligation to the great number of general practitioners who care for the majority of American infants and children. This Section should continue in an active manner to present programs which will attract more men in all the branches of medicine so that it may have a regular attendance at its meetings of as large an audience as any Section. In former years this was so of this Section.

Read before the Section on Pediatrics at the 105th Annual Meeting of the American Medical Association, Chicago, June 13, 1956.

A medical organization which marks time today is retrogressing. Our Section should constantly consider means of attracting capable and interested members. I observe that of the great number of men being yearly qualified to practice pediatrics, very few attend these Section meetings, and fewer still are interested in its workings. The future of the pediatric Section depends on its future membership and I feel strongly that some effort should be made to attract these men into the meetings and to interest them in the activities of this Section. Those now participating in the activities of the Section should invite the younger men in their communities to these meetings. The Executive Committee could send a written invitation to all those men who complete residency training in the various children's hospitals. Younger men in the state societies could be assigned certain things to do for this Section; their appointments being made through their state society. Younger men are active in the state groups; some of them could be interested in the activities of this Section also.

Medicine is a science and an art: an effort to apply scientific knowledge to living people through all phases of growth and development in health and in disease. Medicine deals with the individual from his first newborn cry to his last fleeting breath. The newborn and childhood periods are of interest to practitioners in every branch of medicine. The more representative an organization, the more responsibility it carries. When an organization is elevated to a position of leadership it is expected that it will blaze the way along certain definite lines of progress. It is therefore expected that this Section will assume leadership in matters pertaining to general policies and practices and in the advancement and dissemination of knowledge concerning the health and illness of infants and children.

This Section has a glorious record of past achievement. Its present membership should be sure that present opportunities for usefulness and leadership are not overlooked or neglected. We should emulate our predecessors' example by surveying the field of present day pediatrics and organizing and working out a schedule of labors to accomplish changes or improvement in certain areas where this is indicated.

An example of one current opportunity is the present effort of the American Medical Association to organize work at state level to reduce maternal and newborn mortality. The members of this Section should, in an organized manner, cooperate with the committee of the American Medical Association now working to stimulate the interest and help of state and local medical and pediatric societies in the problem. Our Section could support this effort with papers, discussions, and exhibits designed to spread knowledge of this attempt to improve maternal and child care in all sections of the country.

This Section as such could well exert its influence and support in many of the activities of the state medical and pediatric societies. State pediatric societies should invite and urge into their membership those general practitioners who are interested in child welfare and the diseases of children. The state pediatric society should take the responsibility of participating in the general sessions of the state meetings and not be content to hold only its own section meetings. Each state pediatric society has the responsibility for keeping informed those general practitioners and others in its state whose practice includes pediatric age groups.

The late Dr. C. Anderson Aldrich reported to this Section in 1946 that psychiatrists in World War II found many instances of war neuroses. In the background of many of these was an underlying emotional insecurity dating back to family situations, often as early as babyhood. These and other observations and statements definitely place the problem of mental hygiene within the responsibility of those who treat children. Pediatricians should determine to engage in studies and practices which would serve to reduce the present high incidence of cases of emotional and mental illness in adults.

One area in which progress is being made and which holds great promise for the well-being and better adjustment of future children is in the field of child psychology. At present, students in medical schools generally are better trained in the basic sciences and clinical medicine than in pediatric psychology. When they enter practice, therefore, they are frequently so engrossed in these physical areas that the broad fields of parent and child attitude and the child's reaction to home environment are largely overlooked or neglected until something goes wrong. Considering the present-day concept of the broad field of pediatrics, this area should not be slighted. The people who work with behavior problems in late childhood state that much of their labor could be avoided by a closer survey and treatment of minor situations in early life. This question has wide medical and social implications. Frequently physical and mental ills are so entangled that a clear line of demarcation can hardly be made. A proper appraisal is difficult and at times impossible. The pediatrician is asked about an emotional or behavior problem almost as often as he is asked about malformation, disease, or nutrition. The practitioner should be prepared when he is called upon to answer such questions as, "Should a baby be allowed to cry his way out of an upset or be picked up and soothed and assured?" "When should training for bowel control be begun?" "Should a baby be forced to take a certain amount of formula or, if older, certain foods and how much?" "What should be done about scolding, tantrums, corporal punishment, thumb sucking?"

Scientific answers to problems of physical illness are easy to give, but until more investigation and study of these behavior and training problems are made answers to such questions cannot be based on fact but rather on a little knowledge or on everyday experience. There are sources of learning, and the same teachers in medical schools could teach both. This Section in its programs could interest more pediatric teachers to join the great number of capable workers in this field. Mental disease increases while mortality rates decrease.

Pediatrics is a changing field. Pediatrics has been changing since the first few men became interested in the welfare of babies and children. In 1934, when infant feeding still occupied a large portion of the Section's programs, some observations on clinic patients were reported which showed that of 2000 babies cared for by a Welfare Society, twice as many bottle-fed babies died as did those who were breast fed. These figures would not be comparable with today's and are quoted only to emphasize the progress pediatrics has made in the nutrition and feeding of infants. Also, however, it reminds us that breast milk is a very proper food and that through the ages it has been the safest food. Perhaps breast milk has some growth factor which extends favorable influence long past the nursing age and which also has a protective influence against infection. Today again there is a revival of interest in breast feeding and perhaps this Section might well lend its influence to the support of this interest.

Recently I heard a discussion of the present-day trends in nutrition. The speaker emphasized the propriety of the present-day reemphasis on breast feeding, stated that mixed vitamins are not routinely necessary in the child's diet and that generally children's diets in this country could be improved by a higher protein intake. He also mentioned the present-day necessity for reducing the amount of food taken by certain obese children. Frequently these are obese as the result of overeating, a habit produced by the training of overanxious parents and others who were afraid that the child would be undernourished. Some present-day pediatric situations require the change from "eat more to gain" to "eat less to lose."

Pediatrics distinguished itself by leading in some of the most successful attacks on the problem of human mortality. The success of these efforts has been a major factor in the trend to increased longevity. Generations of physicians have devoted themselves to this great cause. Pediatrics has contri-

buted in the fields of nutrition, foods and feeding, immunizations, the description of newly identified pathologic states, the maintenance of normal fluid and salt balance in many conditions, the pediatric care of surgical conditions, and many others.

We can not yet call this effort finished. We can not yet rest in contentment and think the labor complete when we still have old and new diseases and conditions which plague us and stimulate us to continued effort because of our lack of knowledge of cause, progress and effect, and appropriate and successful treatment. New drugs and techniques and advances in surgery stimulate study in the still numerous conditions which are incurable or uncorrectable. The continuing high newborn mortality and the still higher premature death rate invite more study on the prevention of premature delivery, birth injury, and infections in the newborn period. Some malformations which are today fatal may yet be made to lend themselves to a successful management. The malignancies are still not curable except that some of them may be eradicated if discovered early.

A tremendous opportunity exists to interest ourselves and others in a consideration of those other values, esthetic or otherwise, which must be preserved for the fullest development of medicine. Learning is necessary to keep pace with present-day scientific advances; nevertheless, present-day circumstances demand that science alone is not enough and that some of the characteristics of former years might well be practiced anew. Humanitarianism and patience still must supplement science.

Men in pediatrics have accomplished much in research and practice which has benefitted those in many other specialties and in the general practice of medicine. I think that pediatrics, too, more than most other specialties has retained much of the old philosophy and many of the old practices which people generally expect and appreciate.

Pediatrics came into being because babies and children were being neglected. Their feeding was left entirely to loving but ignorant intentions with no knowledge of requirements, no ability to evaluate deficiencies or upsets, and no ideas of proper food preparation and safeguards. In illness children were treated as small adults and there were no preventive immunizations or any attempt to study or practice child psychology. As the years have passed and pediatrics has grown, it has encompassed all these fields with appreciable progress in each and results which are spelled out in better living for children and much lowered mortality and morbidity rates for all ages.

Shortly after 1929 one of the papers in this Section suggested that pediatrics had served its function and perhaps would no longer be a specialized field of medicine. This statement was based on the fact that at that time much had been learned about infant nutrition and feeding with which pediatricians had largely occupied their energies and also the opinion was unquestionably influenced by the nationwide depression which had much reduced the income of most of the pediatricians in this country.

Since that time, pediatrics has made its greatest strides in many different research and clinical fields and I believe with its present people, knowledge, interest, ability, and energy will continue to accomplish even more at perhaps an accelerated rate, since so many more persons are interested and active in it and men today are better qualified by training than in former years.

In the mechanism which makes progress in pediatrics, two factions, or kinds of people, are concerned—the conservatives and the progressives. The progressives are continually searching in the field of the unknown for facts and conclusions which may be used at diagnostic or clinical levels with improvement to the child. The conservatives are satisfied to consolidate known facts and apply them to the patient. They constitute the analytical segment of the practice and determine the value and practicability of discoveries and changes. Pediatrics is still well supplied with both of these types of mind and a combination of these two is

bound to mean progress. Progress will continue because in the entire field of pediatrics one continually senses, as always, a feeling of warm and sincere cooperation. The will to learn and the willingness to do are still with us. Pediatrics will continue and will grow in size and accomplishment. It is my sincere belief that this Section on Pediatrics will continue to do its part and that it will grow with pediatrics.

Le Bonheur Children's Hospital, Adams at Dunlap.

THE ASTHMATIC CHILD

Development and Course of Asthma in Children

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In outlining the development and course of asthma in children it is important to emphasize that, although asthma is a common illness, it is not a reportable one, and therefore its true incidence is unknown and can only be estimated indirectly. Our impressions of its frequency come from a variety of sources, none of which are comparable groups. These range from local surveys, army inductee examinations, hospital admissions, to sickness surveys of special groups. Dublin and Marks,[1] in summarizing all available statistics, in 1946, state that the incidence appears to be 0.5% for all ages for the entire country, or more than 500,000 persons excluding those who have recovered. Representative examples of these statistics are shown in Table 1.[1-6]

TABLE 1.—*Incidence of Bronchial Asthma in the U. S.*

Investigator	Date	Source	Rate/1000
Dublin-Marks[1]	1946	Estimate all ages	5.0
Rountree et al[2]	1942–1943	World War II	7.5
Bigelow & Lombard[3]	1929–1931	Massachusetts	3.1
Rackemann[4]	1931	Clinic admissions	5.0
Collins[5]	1928–1931	18 states	4.2
Sydenstricker[6]	1921–1924	Hagerstown, Md.	4.1

Compiled from literature (References 1-6).

Studies of the incidence of asthma in children and young people are even more meager than for adults. The sickness survey of Collins[5] for 18 states reports rates of 3.3 per 1000 at less than 5 years, to 4.5 per 1000, at 5-9 years. Sydenstricker,[6] studying Hagerstown, Md., in 1921-1924, found a rate of 5.3 per 1000 in 10-14-year-old children. London,[7] reporting on the composition of a pediatric practice in 1937 and again in 1951,[8] found 6% asthmatics among 1500 children. Kraepelien[9] in 1949-1950 found an incidence in school children of 0.73% in Sweden as a whole, based on health reports, and of 1.3% in Stockholm, based on medical examinations. In other words, from a total of 685,000 children there were 5700 asthmatics. Sheldon[10] found that 9% of 2000 University of Michigan students stated on health questionnaires that they had had asthma. This figure had not yet been verified by personal interview or examination. During 1955, there were 2951 first visits or admissions on Pediatrics at Duke University Hospital. Among these 274 asthmatics were seen, a ratio of 9.3% of all pediatric admissions (Table 2).

Fragmentary as these figures on incidence are, it is evident that asthma is a frequent cause of illness in children, and the relationship of other allergic disorders to asthma becomes important. Here, we are on surer ground, since groups of asthmatic children

TABLE 2.—*Incidence of Asthma in Children*

Investigator	Date	Source	Rate %
London[8]	1951–1952	N. C. pediatric practice	6.0
Kraepelien[9]	1949–1950	Swedish school children	0.73–1.3
Dees	1955	Duke Hospital, N. C.	9.3
Sheldon[10]	1955	U. of Mich. students	9.0
Collins[5]	1929–1931	Sickness survey	0.3–0.45*
Sydenstricker[6]	1921–1924	Sickness survey	0.53†

*Collins[5] rates per 1000, 18-state survey under 5 years., 3.3; 5-9 years, 4.5; 10-14 years, 3.1.
†Sydenstricker[6] Hagerstown, Md. 10-14 yrs. 5.3 per 1000.

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Read in the Symposium on the Asthmatic Child before the Section on Pediatrics at the 105th Annual Meeting of the American Medical Association, Chicago, June 14, 1956.

have been carefully studied from this point of view.

Eczema, which is often the first recorded allergic manifestation, has been related to subsequent asthma by many observers. A summary of several such reports is shown in Table 3. The most detailed studies are those of Glaser,[11] who found that 53% of eczemas progress to asthma, and Ratner [12] who reports 59% of patients with eczema develop upper respiratory allergy and asthma.

TABLE 3.—*Patients with Eczema Developing Asthma*

Authority	Source	Per Cent
Glaser [11]	N. Y.	53
Ratner [12]	N. Y.	59
Kraepelien [13]	Sweden	66
Sheldon [14]	Michigan	60
Tuft [15]	J.N.H.A.*, Colorado	32
Deamer [16]	California	30
Clein [17]	Washington	33

*Jewish National Home for Asthmatic Children, Denver.

Since many of the estimates of the incidence of antecedent eczema are based on information in the histories of persons who have asthma, they therefore may not necessarily reflect the percentage of children with eczema who will ultimately develop asthma. In an attempt to answer this question, we reviewed the histories of 239 children who were seen at Duke Hospital during the period of 1930 to 1945, in whom the initial diagnosis was atopic or allergic eczema. Seventy of these children, or 30%, have subsequently developed asthma. In Table 4 the cases are divided according to the length of time they were followed. One-eighth of those followed only six months to one year developed asthma. One-third of those seen from 1-3 years after onset of eczema developed asthma, while approximately ⅓ of those under observation from 3 to more than 15 years, became asthmatic. On the basis of the ages, when asthma developed in the group followed the longest period of time it is apparent that asthma is not definitively diagnosed in many instances until 5-8 years of age. Therefore, in this series, the time span of the hospital record is not adequate to cover all of the period when asthma would be most likely to develop. Since more than half of the patients (151) have records covering less than five years, the actual incidence of asthma in this group is greater than 30% if one adds to it the number who have reported subsequent asthma by follow-up letters, but which does not appear as a hospital diagnosis. There seemed to be a trend for asthma to develop earlier in the infants whose eczema began before or by 3 months of age than in those with later onset of eczema, but the series was too small for this to be significant statistically. Among 53 eczemas followed 10-15 years or longer, a total of 25 developed asthma. Nine patients had asthma by 2 years of age, seven more became asthmatic by 5 years, and an additional nine developed asthma from 6-14 years of age. The ages when last seen ranged from 10 years in the two younger patients, to 28 in the eldest, with most of these people being in their late teens or early 20's.

TABLE 4.—*Patients Developing Asthma, Allergic Rhinitis Among Two Hundred Thirty-Nine Children with Eczema*

Years Followed	Patients	Asthma	Rhinitis
0-½	36	3	2
½-1	41	6	2
1-2	30	10	5
2-3	22	7	2
3-4	16	7	5
4-5	7	3	1
5-10	34	15	11
10-15	53	25	15
Total	239	70	43

There were 30.5% of all children with eczema who developed asthma during period of observation. Allergic rhinitis developed in 6%. Duke Hospital series 1930-1945.

From unselected hospital records, it is more difficult to evaluate the role of allergic rhinitis as an antecedent to asthma. Referring again to Table 4, we find that 6% of these eczematous children were diagnosed as also having developed allergic rhinitis. We felt obligated to note only official coded diagnoses, in spite of our own impressions that in many more patients the repeated and continuous afebrile upper respiratory infections recorded were actually in most instances allergic rhinitis. From other sources, Glaser [11] in particular, we find that

42% of 149 cases of upper respiratory allergy progressed to asthma.

The most challenging condition, asthmatic bronchitis, bronchiolitis, or tracheobronchitis, as a forerunner of asthma could not be analyzed from our hospital records, since the diagnoses were made by different persons whose criteria were so varied that the patients formed no homogeneous group. Watson [16] recently reported on 23 children with asthmatic bronchitis, out of London's original group of 1500 patients. Eight of these (40%) developed asthma in a five to seven year follow-up; five additional patients would be considered mild allergics who had wheezing with respiratory infection but who were not so classified in London's original study.[7] Deamer [15] states that he would expect 100% of those children diagnosed as having asthmatic bronchitis in his service to develop asthma, since he believes that the condition leading to this diagnosis at the time it was made was in effect asthma. He would expect 10% of children with tracheobronchitis or bronchiolitis to show asthma subsequently. If wheezing was one of the symptoms associated with these conditions he would expect the incidence to increase to 20%-30%. Tuft reports that 10 of the 135 chronic asthmatics now at the Jewish National Home for Asthmatic Children in Denver give a history of asthmatic bronchitis in infancy.

The role of colic lends itself even less well to analysis because of its inherent nature, the subjectivity with which it is diagnosed, and the apparent varying incidence in different types of clinical material. In our experience, based on patients who attend a Public Well-Baby Clinic, colic is seen so infrequently, that one would not anticipate that there could be an appreciable incidence of asthma in such a group. On the contrary, in the same hospital, on reviewing the histories of both public and private asthmatic patients, colic is frequently reported as being a most impressive and distressing symptom in early infancy. It should also be noted that Clein [17] finds colic in 23% of 100, and Glaser in 21.7% of 516 allergic children. Glaser [11] emphasizes that this should not be interpreted to mean that he considers "colic to be always or even commonly, an allergic disease."

There seems to be general agreement that eczema is a frequent antecedent of asthma and that allergic rhinitis in early childhood is also the forerunner of asthma in a high percentage of children. Asthmatic bronchitis and colic because of their nature are assigned varying importance by different observers, but all agree that they are frequent early complaints in children who subsequently have major allergy.

The course of asthma in childhood is surrounded by as much controversy and uncertainty as is its incidence. The opinions range from those who firmly believe that all children outgrow asthma, to those who are doubtful if an appreciable number ever lose this affliction. The most detailed study available at present is that of Rackemann and Edwards,[18] who in 1952 reported a follow-up study of 688 patients after an interval of 20 years. The patients are divided into two groups, 449 seen before 13 years of age, 239 seen after 13 years of age. The results in both groups are analyzed on the basis of the original cause of asthma—animal, food, pollen, mixed, and unidentified, and those with negative skin tests. In Table 5 are shown a portion of Rackemann's, Flensborg's,[19] and our figures. Of the children seen before 13 years, 30.7% are entirely relieved, apparently "cured" according to Rackemann. Another 19.3% were still sensitive but had no symptoms because they avoid the cause, while an additional 21.4% no longer have asthma, but another form of allergy, usually hay fever, had replaced it. This means that nearly three-fourths of the children no longer had asthma by their teens, of the remaining one-fourth who had symptoms, 15% were mild, and less than one-eighth, or 10.9%, had serious trouble. Four of the group died of asthma, a mortality of less than 1%.

Rackemann feels that asthmatics seen after 13 years of age represent a more

TABLE 5.—*Follow-Up Studies of Asthmatic Children*

Authority	Age, Years	Total % Patients	Cured	Relieved	Asthma		Deaths
					Mild	Severe	
Rackemann	<13	449	30.7	19.3	15	10.9	1
	>13	239	21.7	25.5	12.1	44.7	2.5
Flensborg	<14	298	40*		54		1.7
Dees†	<14	236	44		36	20	1

*44% of these had exertional dyspnea.
†Duke hospital series of treated asthmatics.

serious form of the disease, and the results reflect this impression. Of 239 such children only 21.7% were considered "cured," 25.5% were relieved but still sensitive, 8% were relieved of asthma but had other allergies. Mild asthma persisted in 12.1%, severe asthma in 44.7%, 12 of the group died, 6 probably of asthma (2.5%).

Rackemann also states that the typical sequence of events is eczema in infancy due to foods, especially egg and cow's milk; asthma in childhood from dusts, especially animal danders, and later hay fever from pollens. Treatment consisted of avoidance, desensitization to dusts, pollens, animal danders, and dietary restrictions in addition to general hygienic measures.

We have attempted to follow the course of the first 269 asthmatic children who were seen in the first five years of our Duke Pediatric Allergy Clinic. At the end of that period, 33 had dropped from contact. Of the remaining 233 patients who were treated with desensitization, avoidance and dietary restriction, 104, or 44%, were considered to be doing well after two years of treatment, having essentially no asthma. Eighty-six, or 36%, were improved but were still having moderate difficulty requiring some, but much less, symptomatic medication than before they attempted an allergy program. Forty-six or 20% were unimproved. Ten- and 15-year revisions of these results, by follow-up letters, are incomplete at present, but from the replies at hand we believe the ratios will be essentially unchanged.

In 1946 Flensborg [19] reported the results of a survey of 298 asthmatic children who had been seen in two Danish children's hospitals between 1926 and 1939. He found that the majority of cases begin before 5 years of age. In 120 (40%) the attacks had ceased, 15 had died, 5 (1.7%) of asthma. One hundred sixty-three (54%) constantly had attacks of asthma. Of the patients whose attacks had ceased, 41.7% reported that cessation was due to removal or to sanitation of lodgings. In 139 (46%) school attendance was seriously interferred with because of the disease. Of the 116 patients who continued to have asthma after 15 years of age, 33.6% had to choose special professions because of their disease.

In these children treatment is said to be nonspecific, but the measures to which patients and author attribute principal improvement are environmental changes and sanitation and, in a few instances, to dietary measures. No desensitization therapy was used in these children. There are more than twice as many children (54% compared to 26%) still having asthma in Flensborg's series as compared with those in Rackemann's; in addition, nearly one-half of the 40% "cures" report significant exertional dyspnea. There are more than twice as many asthma and nonasthma deaths in the "untreated" group.

It is hardly fair to compare the Rackemann study with that of Flensborg, since the latter was done in a country which has no ragweed pollen, an important allergen with us, and since it was not carried out on the basis of precise differentiation of cases as was Rackemann's.

It is obviously impossible to obtain an accurate long-term follow-up of untreated asthmatics, since they are rarely seen by physicians. In most instances these cases must represent milder forms of the disease, since appreciable difficulty in breathing sends people quickly to the physician for aid.

The mortality from asthma tends to be ignored, possibly because we are still influenced by Osler's aphorism, "the asthmatic pants on to a ripe old age." We are inclined to forget that asthma can be a fatal condition. How important it is, in relation to other causes of death can be learned from the U. S. Vital Statistics for 1953 [20] (Table 6). Deaths from all causes were 1,517,541, from asthma 6737. Comparing this number with other well-recognized causes of death, we find, for example, motor vehicle deaths, 37,955; cancer of breast, 20,566; pulmonary tuberculosis, 16,566; homicide, 7649. If we consider asthma as a potentially preventable disease and compare the 6737 deaths from asthma with deaths from those diseases to which our children are particularly subject and for which we have made concerted efforts at prophylaxis and prevention, we find diphtheria, 156; pertussis, 270; typhoid, 52; bacillary dysentery, 337, and accidental poisoning from barbituates, 337, and acetylsalicylic acid, 98 (Table 7).

TABLE 6.—*Deaths in U. S., 1953*

All causes	1,517,541
Motor vehicles	37,955
Cancer { Breast	20,566
Cancer { Prostate	12,595
Pulmonary TBC	16,566
Homicide	7,640
Asthma	6,737

From U. S. Vital Statistics, Vol. 2, 1953.

TABLE 7.—*Deaths Due to "Preventable" Diseases in U. S., 1953*

ASTHMA	6,737
Diphtheria	156
Pertussis	270
Typhoid	52
Bacillary Dysentery	337
Accidental Poisoning	
Barbiturates	337
Acetylsalicylic acid	98

From U. S. Vital Statistics, Vol. 2, 1953.

In order to further emphasize the relative importance of asthma as a killer, it is interesting to compare deaths from asthma with deaths from certain other diseases for which there are current campaigns and educational efforts for study, prevention, and relief. Again referring to the U. S. Vital Statistics for 1953, we find deaths from leukemia, 9918; congenital malformation of the cardiovascular system, all types, 8725; asthma, 6737; acute poliomyelitis, 1450; rheumatic fever with heart involvement, 1274 (Table 8).

TABLE 8.—*Deaths in U. S., 1953*

Asthma	6,737
Leukemia	9,918
C.V.S.*	8,725
Polio acute	1,450
R.H.D.†	1,274

*Congenital Malformation Cardiovascular System.
†Rheumatic Fever with Heart Disease.
From U. S. Vital Statistics, Vol. 2, 1953.

Since these figures include all ages, for our present discussion we must separate the mortality in the young persons from the over-all number of deaths. We find a total of 243 deaths in persons under 20 years of age from asthma in the U. S. in 1953 (Table 9). Of this number there were 160 under 5 years of age, and 80 under one year of age.

TABLE 9.—*Asthma Deaths, Under Five Years, U. S., 1953*

Total	160
<1 yr	80
1 yr	28
2 yr	24
3 yr	15
4 yr	13

From U. S. Vital Statistics, Vol. 2, 1953.

Deaths from asthma, numerous as they are, do not give us a true picture of the importance of the disease. We have only vague estimates of its crippling effects and of its genesis in childhood, since morbidity from asthma is not a reportable condition. No statistics are available from the Bureau of Vital Statistics, from State Boards of Health, or from the major life insurance companies concerning illness from asthma.

In conclusion, we believe that many reports show that eczema and allergic rhinitis are of serious importance in young children as being forerunners of asthma in 30%-60% of patients. For this reason, these conditions should be treated promptly and vigorously. Asthma has an impressive mortality, and an even greater morbidity, al-

though inaccurately evaluated at present. Incomplete as our information is at present, it is obvious that asthma kills five times as many people as polio, for example, and undoubtedly incapacitates as many, if not more. One of the greatest advances in the understanding and control of this great economic and health problem could come from accurate statistics on its incidence and prognosis. This can be achieved only if asthma and other allergic conditions are made reportable morbidity diseases. A concerted effort by this medical group to bring this into effect could do much to rectify this area of our ignorance.

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The Diagnosis of Asthma in Infants and Children

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In this discussion the term asthma means an allergic reaction in the bronchial tree, a clinical entity with characteristic symptoms, signs, and pathology.

Infectious asthma must be fitted into the picture and just how this is to be done is not clear. Some believe that an allergic reaction in the bronchi is caused by bacterial products. Others would claim that the bacterial action is irritative and is an additional factor in increasing a previously existing allergic reaction or a potential allergy. Under both hypotheses infectious asthma is at least partly due to an allergic reaction.

The diagnosis of asthma should depend ideally on three criteria: has the patient recurrent wheezing, has he definite signs of the allergic state, and does he have no other condition which could cause the wheezing.

According to the first test, the patient should have recurrent wheezing. Wheezing means prolonged expiration with musical sounds and rales. Usually this wheezing is so typical that there is hardly any chance for mistake. Sometimes, however, especially in babies, the wheezing is not typical. It consists of a noisy, difficult breathing, in which the wheezing sounds, if present, are drowned out by loud rattles. It would seem in this condition that the disturbance is largely in the larger bronchi and trachea. These are the cases which need careful study, since the difficulty may be due to causes other than allergic disease. Also we have patients who wheeze or have respiratory difficulty continuously, not in recurrent cycles, and in these also we need to be sure that nothing else is causing a disturbance. These continuous cases are the ones that are most likely to be due to some nonimmunologic cause such as a foreign body, congenital anomaly, or pulmonary infection. To sum up, the recurrent wheezing may be so typical both in history and physical examination that the diagnosis is obvious; or the wheezing may be atypical or continuous so that the diagnosis can only be made by establishing the allergic state and by carefully ruling out other disease conditions.

In the second place, we should try to demonstrate the allergic state, and this requirement is fulfilled by finding one of the following conditions. A clear history of atopic eczema in the past or the finding of this at the present time is satisfactory. Hay fever, as shown by its seasonal occurrence, or any allergic rhinitis which can be clearly recognized by its appearance, skin tests, or eosinophilia in the nasal secretions is also sufficient. Positive scratch tests if they are sufficiently large may be considered good evidence, as also may be a pronounced eosinophilia in the bronchial secretions. The allergic reaction may sometimes be shown by exposing the patient to the inhalant or food and thus producing the symptoms.

Corroborative findings which are not so definitely diagnostic are useful in backing up a diagnosis where the direct evidence is weak. Such would be a history of hay fever or asthma in the immediate family, a past history of severe colic or vomiting in infancy, and a blood eosinophilia of more than 4%.

In the third place, we must rule out other causes of respiratory difficulty. When there is typical wheezing which occurs in attacks, with complete clearing between the attacks, it would seem sufficient to take an x-ray of the chest, do a differential blood count and tuberculin test. When the wheezing is not

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so typical, we must be more careful to rule out other disease, and among these the most important are pertussis, pancreatic fibrosis, foreign body in the trachea or bronchus, and pressure on the trachea or bronchus by a gland or by a vascular ring.

Whooping cough in the first two years of life may be difficult to distinguish from asthma or bronchitis in an allergic child. I have had more trouble with this differential diagnosis than with any other. Among immunized babies, whooping cough is often very mild and, owing to the inflammation of the smaller bronchi, may have an expiratory wheeze. Allergic babies not uncommonly have a spasmodic cough. To further confuse the situation it is not at all uncommon for asthma to appear for the first time after an attack of whooping cough.

Theoretically, the diagnosis of pertussis should be made by the cough plate or pharyngeal culture and the blood count. Actually we are often compelled to treat the patient symptomatically and with antibiotics, and make a definite diagnosis later.

Pancreatic fibrosis occasionally causes respiratory difficulty with musical sounds and prolonged expiration. Bulky and foul stools or malnutrition should suggest this condition, and the diagnosis is then not difficult. In at least two instances asthma and pancreatic fibrosis have been encountered in the same patient.[1]

A foreign body in the trachea or bronchus should be thought of in every case of wheezing in an infant or child. This is especially important when the course of the disease or the type of wheezing is not entirely typical of asthma. From personal experience I can cite one case that is of interest. This child was known to have hay fever, but the wheezing came from a chicken bone in the bronchus. This illustrates a very obvious fact that the presence of allergy does not rule out other disease.

The history, the physical examination, and the x-ray and fluoroscope will usually make clear the presence of a foreign body, but in case of any doubt we should rely on the bronchoscope.

An enlarged gland pressing on the bronchus is said to be an occasional cause of wheezing. I have not seen this so cannot discuss it. I have seen three babies that had been treated for thymic asthma. In each case the baby had clearly demonstrable severe allergic asthma, and it seems probable that the symptoms had nothing to do with the thymus gland.

A double aortic arch forming a vascular ring and constricting the trachea and esophagus was first reported by Gross.[2] This condition may cause stridor and wheezing. I have not seen this, but it is reported that an x-ray taken with a barium swallow will reveal the constriction. Bronchoscopy or iodized oil (Lipiodol) in the trachea will also demonstrate the defect. This condition should be ruled out when the wheezing is accompanied by stridor and is continuous.

Asthmatic bronchitis is a term in very frequent use. We see many babies in the home and in the hospital that wheeze with colds. If a baby has repeated wheezing with colds, this is probably asthma and if so deserves that term rather than asthmatic bronchitis. It is not at all uncommon to see an older child with asthma who is said to have suffered from asthmatic bronchitis for several years and who then suddenly became worse, sometimes as the result of a whooping cough or pneumonia, and who is now obviously a serious case of asthma. It is true that many babies who wheeze stop having their symptoms after a period of one or more years; but, on the other hand, an appreciable number of them get rapidly worse and become severe asthmatics, some of them the intractable type which are so terribly difficult to treat. When we see a baby that repeatedly wheezes with colds, we ought to try very hard to make a diagnosis, and if we cannot make a diagnosis we should treat the condition as asthma for the time being, and if it continues we ought to be able to confirm the diagnosis.

This thesis that babies who wheeze with colds are truly asthmatic is difficult to prove positively. I have the records of 76 such babies that have been followed for more

than two years and most of them from 5 to 10 years. These babies were all treated for asthma.

Exactly half of them have wheezed sometime during the last year of the follow-up. Of the six that had severe eczema and positive skin tests, all are still wheezing. Of the 18 with mild eczema and some positive skin tests, 14 are still wheezing, and of 18 with no eczema and negative tests 11 are perfectly well. The prognosis seems to depend very largely on the degree of sensitization.

However, on observing these babies and their reaction to medication, to hospital admission, and to desensitizing injections, it seems highly probable that they are suffering from the same disease, although in a different degree of severity.

Two questions remain to be answered: Can an infection cause asthma without any inhalant or food allergy being active? When an infectious agent seems to produce the symptoms, is it producing them as an allergen and acting by the allergic mechanism? The whole question of bacterial allergy and how infection causes asthma is very confusing and hard to understand. This is not the place to go into any long discussion of bacterial allergy. It is evident that infection does cause wheezing, but my own idea would be that probably these patients have some other allergy, possibly house dust most frequently, and the infection is an added factor which brings out the symptoms.

An occasional patient will show typical asthmatic wheezing which seems to be due entirely to some condition distinct from the allergic process. For instance, I have seen one child with rheumatic heart disease and cardiac insufficiency who had typical wheezing. We see patients whose wheezing seems to be due entirely to emotional stress, and it is reported that typical wheezing may result from pressure of a gland on the trachea. In some of these patients allergies are evident, in others they cannot be clearly shown; but it would seem to me most probable that when we get this typical wheezing from apparently nonimmunologic causes, there is an allergy of the bronchi which is increased and made evident by these other causes.

To sum up, the diagnosis of asthma ideally depends on three criteria, the presence of recurrent wheezing, the demonstration of the allergic state, and the absence of other conditions which could cause respiratory difficulty resembling wheezing. Sometimes the wheezing is so characteristic that the diagnosis is obvious. Sometimes the wheezing is not so typical, and other tests must be used. In studying the child with respiratory difficulty it is necessary that the nonallergic causes be borne in mind, and that studies be made that are appropriate to the individual case. In pediatrics asthmatic bronchitis is not a useful diagnosis; when a baby or child has repeated or continuous wheezing, a definite diagnosis should be made if possible, and if this is not possible a provisional diagnosis should be made and the patient treated for asthma.

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The Etiologic Diagnosis of Asthma in Childhood

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In other fields of medicine symptoms are grouped into complexes or syndromes in order to arrive at a working diagnosis, even though the cause of the suspected malady is incompletely understood. A specific etiologic diagnosis is essential for the proper management of asthmatic patients. This becomes of utmost importance when one realizes that the "cure" of this condition lies in its prevention and this becomes possible only when every factor that influences the course of the disease is known and controllable. The word "cure" is used here in its clinical or symptomatic form, rather than in its absolute sense, since the genetic characteristics of the allergic state is a birth right that cannot be altered. The investigative work necessary to identify the etiologic agents in cases of asthma may be termed an allergy survey.

Considerable confusion exists regarding the meaning of the term allergy, and it might be well at this time to discuss and define the term as it will be used throughout this presentation. As originally used by von Pirquet,[1] allergy referred to a "changed reaction capacity which the human or animal organism gains through recovery from disease or through treatment with foreign substances." Knowing nothing of the presence of antibodies or their causative role in the condition under investigation, von Pirquet, it seems clear, was referring to a bodily response rather than to its underlying cause. It is in this sense, then, namely a tissue response, that the term allergy is used throughout this paper. Table 1 demonstrates this point graphically. The tissue alterations of edema, hyalinization of the mucous membrane, and loss of hemogeneous ground substance in the connective tissue give rise to the asthmatic symptoms of cough, dyspnea, and wheezing, which generally respond to specific groups of drugs (sympathomimetic, antihistaminic, steroid, and corticotropin [ACTH]) despite the fact that diverse factors may be responsible for its production. Thus, asthma of psychic origin cannot be differentiated clinically or histologically from that due to pollen or food. Under such a concept asthma becomes a clinical entity produced by multiple and diverse factors.

A complete allergy survey includes a history, a physical examination, laboratory studies including skin tests, clinical trials, and diary. The history is usually the focal point of inquiry and the one that is given primary consideration, for the amount and the direction of all other studies will depend on the information gathered from this source. This requires the most detailed type of inquiry into all the possible factors that are known to influence the course of childhood asthma. In order to depict the nature of the principal etiologic factors the arbitrary classification is presented in Table 2. All the possible etiologic agents have been divided into the immunologic and nonimmunologic. It is not to be inferred from this that the etiology of asthma is divisible into such sharp categories. The causal pattern of the average case of childhood asthma is usually mixed and contains factors from both groups. The classification serves only to indicate the type of investigation necessary to identify the etiologic agents in each category.

From the Allergy Clinics of Temple University Hospital and the Albert Einstein Medical Center.

Read in the Symposium on the Asthmatic Child before the Section on Pediatrics at the 105th Annual Meeting of the American Medical Association, Chicago, June 14, 1956.

TABLE 1.—*Concept of Allergy as a Tissue Response*

Tissue Changes	Symptoms	Therapeutics	Cause
Edema	Cough	Sympathomimetics	Infections
Hyalinization	Expectoration	Antihistamines	Foods
Loss of homogeneous ground substance	Dyspnea	Steroids	Drugs
Hypertrophy of bronchiolar muscles and mucus glands	Wheezing	Corticotropin	Pollens
			Inhalants
			Meteorologic
			Endocrine
			Psychic

As previously indicated, the history is by far the most important part of a diagnostic survey in childhood asthma. It is here that one begins to associate symptoms with the time of the year and a possible pollen or mold factor, with proximity to domestic pets like cat and dog, with the ingestion of a specific food, with respiratory infections, or with physical factors of laughter and overexertion. Some difficulty may be encountered in obtaining a sufficiently detailed history in cases of asthma of relatively short duration. This is entirely understandable since clinical observations were limited to a few attacks where cause and effect relationships could not be demonstrated. In such instances one must continue to observe the patient and wait for the pattern to unfold itself. History-taking is never completed until one is satisfied that he has uncovered each and every factor that influences the course of the disease.

TABLE 2.—*Classification of Etiologic Factors in Asthma*

Immunologic	Nonimmunologic
Foods	Infections—upper respiratory
Inhalants	Meteorologic factors—dampness, temperature changes, drafts, airconditioning
Molds	Physical factors—exertion, overeating, laughter, and teething
Pollens	Psychic
Drugs (?)	Physical allergy
	Bacterial allergy
	Powders, volatile gases, smoke and odors
	Endocrines—puberty, menses, pregnancy and menopause

Where the history suggests an immunologic factor, skin testing is usually indicated. A word of caution should be issued regarding this procedure, not so much because of the dangers inherent in it, but because of the inability of many to properly assess and interpret them. The novice who is incapable of properly interpreting such tests should not perform them. The prime purpose of performing skin tests is to detect skin-sensitizing antibodies. These are the heat-labile antibodies that have great affinity for mucous membranes and that are transferable to human skin through the Prausnitz-Kustner technique. In the evolution of the allergic state, the skin-sensitizing antibody is usually one of the first things to appear. This occurs long before there is a shock organ or clinical symptoms. The process of sensitization may become arrested soon after the appearance of these antibodies, and clinical symptoms may never ensue. Under these circumstances a positive skin reaction indicates potential sensitivity. The skin test remains positive for many years after spontaneous remissions have occurred. Skin reactions persisting after clinical remissions indicate past sensitivity. A positive skin test in the presence of a clinical history indicates present sensitivity and, as such, is of etiologic importance.

One is constantly queried about the number of tests required for a complete study. Let me state categorically that there is no fixed number of tests that serves this purpose. It is a good rule to limit testing to the smallest number that will yield the desired information. Generally this should include the principal articles found in one's environment and diet. An effort should be made to individualize testing rather than subject all patients to a formidable and fixed testing routine. Furthermore, skin testing is indicated only in those cases where an immunologic factor is suspected.

The relative merits of the scratch and intracutaneous tests deserve some considera-

tion and comment. Most allergists utilize the intracutaneous type of testing exclusively. Others prefer to do a preliminary survey by the scratch method and retest selected negatives by the intracutaneous method. The option is a personal one depending upon one's indoctrination and office routine. It would be best to become proficient in and adhere to a single type of testing. This would circumvent the need for multiple testing equipment. The scratch and intracutaneous methods of testing are both capable of detecting skin-sensitizing antibodies. The intensity of skin reactions is in direct proportion to the titer of antibodies.[2] The scratch tests are less sensitive, safer, and more specific than the intracutaneous. As such they may often fail to demonstrate low titers of antibodies. Where they do react positively, they are more specific because they correlate better with the clinical history. Where reactions are very intense, the superficially applied antigen may be removed easily, preventing further absorption and avoiding the possibility of constitutional reactions. The antigens used in scratch testing are concentrated, do not require refrigeration, do not deteriorate, and are relatively inexpensive. Scratch testing requires a minimum amount of equipment to perform, and a large number of tests may be done at a single sitting. The opposite holds true for the intracutaneous type. It is for these reasons that the scratch test has become the one of choice for those doing a limited amount of testing.

The longer one practices, the more profound becomes his respect for the ability of skin tests to demonstrate antibodies in clinically sensitive patients. The instances where the skin tests are negative and do not correlate with the clinical history are not a reflection on the inadequacy of the test. Negative reactions of this type merely indicate the absence of antibodies to the tested antigen. Hypersensitivities to products of digestion have been recorded and positive reactions obtained when the proper antigen was prepared by partial digestion.[3] Despite this high degree of specificity, instances may occur where a positive clinical history is accompanied by negative skin reactions. This is attributable to our inability to synthesize the complete specific antigenic molecule. One must continue therefore to search for this antigen while eliminating the offending agent from the patient's environment. This is especially true in drug allergy where skin reactions are almost always negative even though the history is unequivocally positive.

The identification of factors in the so-called nonimmunologic groups is much more trying and time-consuming. Each investigator develops his own approach to such problems. The one that has proved most useful in my experience is one that permits the patient to gather such information through a diary. Notes are made only when symptoms appear or become exaggerated. Attempts are made to associate symptoms with every phase of one's environment. Rather than permit the patient to flounder through a maze of meaningless factors, they are given direction by calling their attention to specific areas where such culprits usually reside. Table 3 enumerates these areas.

TABLE 3.—*Method for Keeping Diary*

Associate symptoms with:
1. Environment and activity at time of attack
2. Foods and drugs ingested or contacted
3. Meteorological conditions, including temperature changes, drafts, and airconditioning
4. Puberty, menses, pregnancy, and menopause
5. Infectious states
6. Physical tiredness due to lack of sleep, overwork, and overexertion
7. Emotional states

The gathering of information by this method has several obvious advantages. First and foremost, it places the physician in the position of a judge who listens and evaluates all the evidence presented. It also gives the patient a clearer idea of the amount and nature of evidence required to establish cause and effect relationship. Each clue is pursued until its causal relationship to symptoms can be proved or disproved. Where the results are not convincing,

further experiments or clinical trials are usually planned by mutual consent. Once a conclusion is reached, treatment follows automatically for its etiologic importance has already convinced the patient of the validity of such a procedure.

It is to be remembered that proof of this type is seldom as convincing as the objective positive skin reactions found in the immunologic cases. Furthermore, exposure by clinical trial is much more difficult to reproduce in the nonimmunologic groups for it often represents conditions and circumstances beyond our control. When information of this type is properly gathered and evaluated, it fulfills all the necessary criteria to demonstrate cause and effect relationship, for, in the end, no agent is to be considered a cause of asthma unless this type of relationship can be proved.

The etiologic picture in childhood asthma is less complicated than in adult groups. Of all the factors listed, infections stand out as the number one offender. It is here that the physical examination and laboratory studies are used to establish the existence of an infectious state. There are some who believe that asthma following infection results from bacterial hypersensitivity. Adherents to this school of thought must explain the lack of correlation between the intensity of the infection and the severity of asthma, the time disparity between onset of infection and symptoms, the duration of asthma long after the infection has subsided, the lack of symptoms from the same bacterial flora present between infections, one's inability to control the asthma by conquering the infection, the poor results from vaccine therapy, and why respiratory infections, almost to the exclusion of all others, seem to be the type that produces asthma. Although antibodies for bacterial extracts can be demonstrated, they are of the delayed reacting (tuberculin) type and give no indication whether the positive reactions are of etiologic significance at this time. Such reactions merely indicate experience or contact with the organism. Information gained from this type of testing is vague and contributes little to our knowledge of the case. It also explains why testing with bacterial extracts has found such limited usefulness.

An allergy survey is not complete until every etiologic factor has been identified and properly assessed. It is for this reason that the survey often continues while treatment is being rendered. Every case of childhood asthma deserves such a detailed study. It is to be remembered that the ultimate aim of an etiologic diagnosis is prophylaxis. When this task has been successfully accomplished, one may liken the pattern to a jigsaw puzzle made up of many parts, of various sizes and shapes, no two of which are alike, yet each having a definite bearing on the final picture.

Having generally indicated the type of investigation required to identify the etiologic agents in the two main categories, let us next dwell on the relative incidence of each in childhood asthma. The impression gained from reading the current literature is that some specific immunologic mechanism is responsible for most cases of bronchial asthma. In clinical practice, however, one finds just as many in the nonimmunologic as in the immunologic grouping. If all asthmas were caused by specific antigens, their diagnoses and management would be a relatively simple matter. Skin testing would invariably identify the culprits, and elimination of these agents from one's diet and environment would serve to avoid antigen-antibody reactions and the symptoms that follow in their wake. A review of the literature at the turn of the century, when little was known about the immunology of asthma, would reveal that many considered asthma a disease wherein a nervous diathesis existed and where catarrh either accompanied or preceded it. The discovery of the immunology for allergic diseases merely added new and previously unknown etiologic agents. It did not necessarily negate all the other concepts.

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The Emotional Problems of Childhood and Their Relation to Asthma

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Since 1946, we have systematically and consistently observed and treated allergic patients within the psychosomatic frame of reference. From this approach we have confirmed that not all occurrences of clinical allergy are caused by allergic reactions or other physical agents but may be set off and continued by emotional causes.[1] We have also come to believe that in asthma there is a constitutional factor,[2] a common denominator, which predetermines this clinical syndrome when it occurs whether from physical or emotional causes.

In a group of 201 clinically allergic children studied, practically all at one time or another had had asthma. Allergy skin tests showed that the great majority were immunologically allergic as well as clinically allergic.

In every instance the parents, sometimes the mother alone but in most instances the father also, were interviewed. The older children were also interviewed, and the younger ones were studied by means of diagnostic doll-play sessions, the "Draw Your Family" technique, and, where indicated, the Rorschach and other psychological tests.

Similar observations were made on a control group of 110 children who had no manifestations of clinical allergy but were being treated for behavioral problems.

Data were sought on children's and parent's life experiences and fantasies which might be related to the psychosomatic pattern. A study was therefore made of acute emotional traumata which preceded the first onset of clinical allergy.[3] It was found that experiences such as overstrict toilet training, threats of punishment for masturbation, the mother going out to work, physical punishment, divorce of the parents, tonsillectomy, and physical accidents often meant loss or threatened loss of the mother to the asthmatic child.

Such experiences in childhood are of course not unique. They are apt to produce the fear of loss of the mother in any child, yet they are not usually followed by physical illness. But allergic children apparently get sick in the way they do because the emotional traumata fall on constitutionally determined and emotionally fertile soil.

To the allergic child these experiences confirm his fear that his mother has not loved him. The realistic basis for this became clear in the psychological interviews with their mothers.[4] Ninety-seven per cent of the mothers verbally expressed their rejecting attitude toward these children, whereas only thirty-seven per cent of the mothers of nonallergic children expressed such an attitude. A significant critical ratio of 9.4 was found.

At first glance it might seem that the burdensome illness of the child could be the basis for the expressed rejection. However, in 96 of the 100 allergic cases there was evidence that rejection had been present before the onset of the child's illness, not after its inception. In two-thirds of the cases, potential rejection was shown to have been present actually before the child was born. As one mother said, "He was an accident. I didn't want him. After he was born, I was always doing something to push him away." Another said, "I was happy

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while I was carrying him. I felt I needed him inside of me and that I'd be angry when he left me. I've been trying to make him part of me ever since." The seed of rejection had thus already been sown, to sprout whenever the child would seek to establish his own autonomy.

How the allergic child feels in such an emotional atmosphere was well expressed by an asthmatic boy, Billy, who said, "She cooks for me what she thinks is good for me. She's always fussing about all sorts of things I should or should not do but she doesn't really pay any attention to *me*."

As the result of these feelings, the allergic child develops an inordinate hunger for affection and anger at not having it satisfied. Yet he is afraid that if he shows his anger he will be further deprived. For this reason he blocks or disguises his anger so that often that he is angry. The parents usually characterize the allergic child as a good child basing this judgment on behavior that stems neither he nor those about him are aware from passivity, dependency, and apparent amenability to imposed regimens. These reactions to his emotional environment, as well as his asthma, are attempts on the part of the child to establish some sort of adjustment to the pressures within him of his greed for affection, his anger at his parents, and his fear of losing their love.

Obviously, the attempt is unsuccessful. It thus becomes the task of the physician to develop techniques in his medical care that will help the child find more realistic and healthy solutions to his problems. These techniques should remain an integral part of the day to day care of the child whether it be in interviews, physical examinations, skin testing, the administration of medicines or immunizing injections, all of which still remain essential to the physical care of the asthmatic. As is evident from what has been said, the parents play an important role in the child's life and the techniques must take them into account also.

All of this poses a difficult problem in practice. On the one hand, the doctor must let the child patient see that his feelings are given response. On the other hand, he must let the mother and father see that their feelings, which are often opposed to the child's, are similarly accepted. Even in the initial interview, the doctor needs to accept the feelings of both parent and child.

As illustration: Mrs. L. complains, "Sophie's terrible, Doctor. She won't take her medicine." Sophie, an 8-year-old asthmatic, stares stonily. The physician nods and says first to the mother, "You have a terrible time, don't you! You get pretty desperate! And at times it makes you quite furious at Sophie," (putting into words the feelings which the mother's facial expression and psychomotor tensions have shown). Then he says to Sophie, "And I guess you get pretty mad at Mother, too, when she tries to force you. It's no fun to take medicine." And to both, "You're both having an unhappy time."

In this manner, the physician establishes himself in the role of a kindly parent to both mother and child. He has lifted the taboo against seeing that hostile feelings are natural. And he has demonstrated to the mother some things she herself will gradually need to acquire, namely, acknowledgment and acceptance of how her child really feels.

Because the mother and father are both important in the child's environment, the physician does well to see each one separately as part of the initial work up. His interest in their childhood, their home, their parents, their siblings, their marriage now and their feelings all along, lets them know they are important as people. It relieves pressure and at times results very quickly in the beginnings of insight. One father recounted, "As a child I'd be so mad at my sister. She got all my mother's time." He stopped suddenly. "That's the way with my child now. My wife's world revolves around her." Then he paused, "You know, Doctor, that's silly, isn't it, for a big man to be jealous of a little girl?" The following week his wife reported that with the new satisfying response this father was giving his

daughter, her incessant demands and her physical symptoms had both decreased.

In connection with a child's physical examination, since fear invariably increases anger, feelings need particular attention. Five-year-old Tommy, for instance, howled at the mere mention of being examined and grabbed tightly onto his mother's skirt. Unwittingly her fist rose for an instant. Then dropped. But the physician caught her feeling. He said in kindly fashion, "Take it easy. It does make mothers angry when their children don't do the things they're expected to." And turning to Tommy, "It makes children mad when they're expected to do scarey things. You're naturally mad now, Tommy, at both mother and me."

With this the mother relaxed visibly and her arm crept around her child. "I guess he is scared," she murmured. And feeling his mother more warmly with him, the child relaxed too.

When it comes to skin testing, children are usually frightened even when they do not show it. Knowing that an unanticipated hurt is harder to take and creates more resentment than one which the child expects, the physician explains beforehand, "These feel like pin pricks. They hurt a little, you know. If you feel like saying 'Ouch,' say it or anything else you want."

Sanctioning such protests, or saying to the child, "If you feel like crying, it's all right to cry," helps the child to get out feelings which might otherwise come out in symptoms. At the same time, however, the physician makes it clear that there are, nevertheless, certain ways in which he expects the child to act.

"I want you to sit as still as you can. I know you don't want to and that you're angry at me for this. But it's necessary to do what I say."

In short, the physician can use with both child and parent a threefold technique which has been applied successfully in aiding asthmatic children to bring out the repressed anger in ways that reduce anxiety and help symptoms clear.

The first step in this technique is to name the feeling, matter of factly, knowing that this feeling is natural. "You feel angry . . ." or "I know you feel mean. . . ." The second step is to name or identify the person toward whom the hostility is felt. "You're angry at me . . ." or "at father . . ." or "at mother." The third step is to name or identify harmless, nonhurtful and nondestructive channels through which the feelings may be brought out. "You may say 'ouch' or 'damn' or cry or scream . . . but you may not run out of the office, or hit me, or jump up and down while I'm doing a test. . . ." In other words, the physician must diagnose and treat feelings and actions as two different symptoms. Feelings must be opened up and drained out. Actions must be controlled and limited so that the child does no harm or hurt to anyone including himself. When he senses that the physician understands him and sanctions his angry feelings, he begins to be less anxious about them. When he sees that he is not permitted to act them out hurtfully, his anxiety diminishes further, so that in cases where repressed anger has triggered the illness it can come out in healthier ways.

Through using these techniques, the physician demonstrates them to the parent, much as a surgeon during an operation demonstrates to the medical student, techniques which he needs to acquire.

It helps too, to explain to parents that the most natural and common target of a child's anger is generally the mother first, with the father at times stepping into the lead. Let the parents know that, since they have been the closest people in the child's life, they are also the objects of his biggest loves and greatest grievances. Therefore in connection with curing the child's illness, the hostility toward them needs to be acknowledged.

In addition it helps if the physician can give the child a few minutes to talk out his feelings without a parent's presence. This relieves the parent of some of the burden of handling the child's hostility and often benefits the parent-child relationship.

To cite an example: Seven-year-old Sam rubs his arm after his injection and stands looking expectant.

"Okay, Sam," says the doctor, "Let's have this week's bothers."

"Well," say Sam, "You see my father, he likes to boss children too much."

"And that makes you mad at him" (identifying both the feeling and its object).

"Uhuh," says Sam.

"Suppose then," says the physician, "that you do a scene for me, like on the TV" (encouraging channelled release).

Sam grins and goes into his act. "My father says, 'Take out the garbage, empty the wastebasket, do your practicing, get the newspaper, shut the door quietly, take the dog walking, take you elbows off the table, and *don't* make so much noise when you chew.'"

The physician nods and encourages, "Show me, too, what you'd like to do."

Sam sniffs. "I want to say 'I'm tired of bossy men who push their kids around. I don't like bossy men.' . . . And then my father says, 'I don't care if the King of England doesn't like bossy men. You've got to do what I say.' Do this. Do that . . . So I get real, real mad and I say, 'What a tie you've got on there! That's not the right tie to wear with that suit!' And then he shouts at me, 'I don't care if this tie doesn't look good on the King of England, it's the one I'm going to wear!'" And then Sam adds with a final rush of feeling, "I'd like to choke him with it around his neck."

The physician answers, "You'd like to. But you know of course that you can't," again naming channels and differentiating, so importantly, between feelings and acts.

Sam grins, grabs for a tissue, blows his nose clear, and goes out.

The whole thing, injection plus talk has taken five minutes.

Along with such procedures, the following measures have also been found efficacious:

1. Reducing nonessential restrictions and demands in the regimen.

2. Removing condemnation from sensory habits such as thumb sucking or masturbation.

3. To have each parent set aside about 15 minutes three or four times a week to be alone exclusively with the child and to spend this time listening to him or doing things he particularly likes.

4. If the child is an infant, to have daily "cuddling" or "rocking" times provided by a parent or parent-substitute who is able to enjoy these with the child.

At the same time, being aware that the child's hostility is often intensified by the mother's inner resentment, the physician will continue to give her times to talk when the child is not present, so that she may ventilate and have her feelings sympathetically accepted and, if it seems indicated, to do this with the father too.

In essence, all along, as an integral part of his medical treatment will go the physician's knowing and showing that human beings need understanding and love.

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The Symptomatic Treatment of Asthma

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The symptomatic or drug treatment of uncomplicated asthma has become fairly well standardized [1-6] and requires knowledge of only about 8 or 10 drugs. In approximately one-third of the asthmatic cases infection is present, and in these the judicious use of antibiotics and other measures is required. These infections are usually secondary invaders on a host made susceptible by allergic edema, and only rarely does a bacterial sensitivity exist. Some of these patients with recurrent asthma due to infection will profit by use of gamma globulin every three to four weeks. Very rarely in the child with the resistant or chronic case or less rarely the case of status asthmaticus may need one of the adrenal steroids to tide them through a severe attack. But all of this does not relieve the physician of the obligation of giving the patient the benefit of a very careful and detailed "work up." A conscientious physician certainly can not pass over his duty by using the much abused statement, "Maybe he will outgrow it." Therefore the following treatment suggestions may be helpful until a careful allergic management can be carried out.

Treatment Suggestions

1. *Bed Rest.*—The bed rest in an allergy-free room should be routine and not too difficult to carry out or expensive (coverings for mattress and pillows would be about $17.00). The air filter or conditioner with filter is not as essential and is costly. However, with some asthmatics the closing of windows seems to be a definite aid. The move to a hospital may be for environmental change as well as for psychological help. The apparent help from a fan may be largely mental, but, unless there is dust in the room to stir up, it is worth trying.

2. *Fluids.*—Adequate emphasis on fluid intake is frequently neglected yet a most important aspect of treatment. Adequate fluids should almost be one of the 10 commandments of treatment in most pediatric problems.

3. *Enema.*—Enemas have clinically proved their usefulness, though their use is often questioned by the mother. Careful and controlled clinical proof has not been shown, so far, but the "feeling from experience" of many well-known pediatric allergists gives basis for the use, and the enema is harmless and helps keep an anxious mother busy. However, do not give repeated enemas as there may be a sodium loss.

4. *Reassurance.*—Reassurance is one of the important parts of the art and practice of medicine and nowhere seems to have as good an effect as in the acutely ill asthmatic. A confident physican who comes into a home and "takes charge" is sometimes "better than a dose of medicine." In some instances, in order to substantiate my clinical impression of a psychogenic element, I have used the patient's confidence in me and given sterile water where formerly epinephrine had been used. If it affords improvement, the psychological element must be given further investigation; if it doesn't, antiallergic treatment can still be given later.

5. *Agents.*—(A) Sympathomimetics: Of the sympathomimetics, epinephrine is the standard and is given in small doses (0.1-0.3 cc. or 1½-5 min. according to age

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and weight) by hypodermic q 15-20 min. until relief is obtained, but not more than three times, and can be repeated in three-four hours. *Do not overdose.* It can be, but seldom is, given intravenously (0.25-0.5 cc.) in 200-500 cc. dextrose. If the patient is old enough (6 years plus) and will cooperate, the 1:100 spray is a substitute "home remedy" to avoid "shots." Two to four deep pharyngeal inhalations with two to three compressions of the bulb can be used and repeated in two to three hours if successful. *Do Not Use* 1:100 by hypodermic. In my hands the 1:100 spray has been a disappointment and has been shown by Benson and Perlman [7] to be irritating to bronchi.

Ephedrine (sulfate or hydrochloride) is very useful orally in early and mild asthma in dosage of ⅛-⅜ grains (8-25 mg.) and is usually combined with phenobarbital in half or similar amount (because of its stimulating effect on the nervous system). In small children, a preparation of ephedrine sulfate syrup N. F. (¼ grain to z.) is frequently used, has a good taste, and can be combined with phenobarbital elixir U. S. P. (also ¼ grain to z.).

(B) Bronchodilators: Among the bronchodilators, aminophylline is the best and most frequently used and is most effective intravenously, but must be given *very slowly* usually in 30-500 cc. dextrose. The dosage is 6 mg. (1/10 grain) per kilogram; but if relief is obtained before the full amount has been given, stop. It is given oftener rectally as a suppository (0.125 to 0.25 gm. —0.25 gm. is infant size) or as a powder dissolved in water as a retention enema. If vomiting occurs, stop or reduce the dose, since this drug is toxic and can be dangerous in overdosage. Intravenously it is the most effective remedy in troublesome attacks where the patient has become resistant to epinephrine. Rectal use will usually not relieve severe attacks.

Isopropyl epinephrine, isoproterenol hydrochloride (Isopropylareterenol), isoprotenol hydrochloride (Isuprel, Aludrine), or isoproterenol sulfate (Norisodrine) is useful at a 1:200 spray or in 5-10 mg. (regular size tablets are 10 and 15 mg.) dose sublinqually where it is held until dissolved. This can be repeated three-four times in 24 hours. It is not usually effective in severe cases.

The antihistamines are of aid mainly in seasonal or pollen asthma only if used very early, and then about 20%-30% of children are helped. The average dose is 1-2 mg. per pound, yet requirements vary with the drug used and from one patient to another. Some of the drugs commonly used are diphenhydramine (Benadryl), tripelennamine (Pyribenzamine), chlorprophenpyridamine (Chlor-Trimenton), theobromine sodium (Thephorin), promethazine (Phenergan), and pyrrobutamine (Co-Pyronil). If used in large doses, the drying or atropine-like effect may be harmful by interfering with expectoration.

(C) Expectorants: Expectorants are used almost routinely in chronic asthmatics, expecially if infectious or "intrinsic." They are also used in acute asthma where sticky mucus or plugs seem to interfere with proper aeration. Those most frequently used are (1) potassium iodide—the best. It can be given as a saturated solution (1 grain per drop). The average dose is slightly less than 1 grain per year of age up to 12 or 15 grains three times a day. Slightly smaller doses are frequently used through the winter and can be kept up indefinitely. The danger from overdosage and rashes has probably been overemphasized. (2) Ammonium chloride can be substituted in acute asthma if there is sensitivity to iodides and given in dosage 0.1-0.3 gm. (1½-5 grains) in some syrup to disguise the taste and given every two-four hours, since the effect is not prolonged. (3) Moisture is another useful expectorant and is preferable in the form of cold vapor mist, if available; otherwise steam may be used. This should be used in a tent or, if only in room, atmospheric saturation must be obtained. (4) Ipecac, in an acute emer-

gency, can be used and is usually given in dosage of ¼-1 teaspoon every 5-10 minutes until vomiting occurs. This helps bring up mucus or plugs for temporary aid.

6. *Antibiotics and Treatment of Infectious asthma.*—It is fairly common knowledge that more difficulty is encountered in treating asthma associated with infection than any other form. Also in status asthmaticus there is nearly always an infection present. In these cases antibiotics and/or chemotherapy have, in many instances, been practically lifesaving even though the so-called "cold" is usually viral in origin and not susceptible to these drugs. If or when used with a "cold," their benefit is from prevention or treatment of the secondary bacterial invaders. However, one must be very cautious and not mistake allergic rhinitis or hay fever for a cold and give antibiotics unnecessarily. This is especially likely in children, since they frequently have temperatures of 100 F or slightly above with noninfectious asthma.

Routinely, where history, physical, and laboratory findings are consistent with an infectious asthma, one of the broad-spectrum antibiotics can be used in full therapeutic dose (10-15 mg/kg. body weight). As soon as there is definite clinical improvement and temperature has remained under 100 F for two to three days, then this dose is cut in half and used for an additional four to five days. In this manner, relapses or chronic infection are usually prevented. If, by temperature drop and clinically, the infection does not respond within two days, another broad-spectrum-type antibiotic is substituted —or penicillin or sulfonamide is used. At the onset, if one suspects a Streptococcus infection clinically (or if this is proved by culture), penicillin is given in the form of a long-acting (four-five day) depository type. Benzathine penicillin G (Bicillin) 300,000 to 1,200,000 units (averaging 10,000 units per pound) is usually used. If bronchiectasis is suspected, penicillin or one of the broad-spectrum antibiotics can be used by aerosol. At the end of five days, if the patient is doing well, oral phenoxymethyl penicillin (V-Cillin, Pen-Vee-Oral, or Vicillin) is substituted; 200,000 units is given every eight hours (6 a.m., 2 and 10 p.m.) for four to five more days, then given once a day, for as long as needed. If the patient is very susceptible to infectious asthma and especially if one or two "bouts" have occurred already, this daily dose of 200,000 units is continued all winter. This use of penicillin (or sulfonamide can be substituted for prophylactic use) is similar to the program outlined by American Heart Association for prevention of rheumatic fever. Of course, along with the antibiotics the other routine asthmatic drugs, as outlined above, are prescribed just as in noninfectious asthma. However, these drugs are not nearly as effective if infection is present as in pure allergic or pollen asthma.

7. *Gamma Globulin.*—This has achieved a place in the treatment of many of the recurrent asthmatics associated with infection. Since Bruton's[8] original article on agammaglobulinemia in recurring infections, the use of this blood fraction in research and in clinical medicine has gained in popularity. Although there is rarely an agammaglobulinemia or even a definite proved (by low blood levels) hypogammaglobulinemia, its clinical use has given good results. Bowen,[10] Berton,[9] and others have reported on its use in asthma. The dosage used is not standardized, but Gitlin[11] recommends 0.6-1. cc. per kilogram of body weight for those with agammaglobulinemia. However, in patients with only a low gamma globulin, half this amount seems to be effective. My present dosage is 1-2 cc. per 10 lb. weight and given every three-four weeks. In prophylaxis of viral diseases even as little as 0.01 cc. per pound seems effective.[12]

8. *Bronchoscopy.*—It is in severe infectious asthma and especially status asthmaticus that therapeutic bronchoscopy finds one of its greatest fields of usefulness. Here it can be used to (1) remove thick tenacious mucus and break up a chronic asthmatic state, (2) remove mucous plug or foreign body causing

atelectasis, (3) dilate stricture if present, (4) remove mucus, pus, etc. from bronchiectatic areas, (5) remove mucus and prevent asphyxiation in moribund patient.[13] This can be done by a skilled bronchoscopist with very little anesthesia (occasionally with no anesthetic) in a very short time and usually with marked clinical improvement. Therapeutic bronchosocpy is being used more and more frequently and is recognized as a definite aid in the prevention of bronchiectasis. The use of a portable exsufflator or coughalator is being tried, but I have not found it too helpful in children—mainly because of the difficulty in getting children to use it.

9. *Corticotropin ACTH, Hydrocortisone, Cortisone, Prednisone, Prednisolone.*—These hormones have given us a new and potent weapon for treatment, but they are still only a temporary aid; they do not cure, and should not be used as a substitute for a complete and thorough history and allergic work-up. My own indications for their use are (1) research, (2) status asthmaticus—not relieved by other standard methods of treatment, (3) moderately severe long-continued asthma where other medications have not given relief sufficient for thorough examination and testing, (4) severe chronic asthma where regular medications have lost their effectiveness and where a short course with hormones may relieve patient and allow for return of the effectiveness of other treatment.

The dosage of cortisone varies from 50-200 mg. a day, in four doses, and depends more on severity of asthma than on age or weight of the patient. After relief is effected, the dose is slowly reduced (12.5 to 25 mg. a day). Great caution should be used in employing these medications in the face of possible chickenpox. These hormones seem to greatly increase the severity of chickenpox and have contributed apparently to fatal outcome in this otherwise usually mild disease.[16]

Prednisone or prednisolone are equally effective and require only one-fourth to one-fifth of the cortisone dose and one-half to one-third of the hydrocortisone dose. Also there is minimal effect on potassium and sodium, and a more liberal diet can be given. However, with prolonged usage, apparently the symptoms and signs of Cushing's syndrome will develop.[14,15] They have not eliminated complications, and the same precautions should be taken as with cortisone. The use of 5-20 units of corticotropin in 100-500 cc. of 5% dextrose by a six-eight hour slow I. V. drip is still an efficient weapon against status asthmaticus if other methods have not given results.

10. *Sedatives.*—In some hospitals it is routine practice for an asthmatic patient to be given a sedative on admission. Yet the old saying "an unattended asthmatic never dies" must have had some clinical background for its existence. There may be psychological reasons as well as the environmental change which prompts many physicians to hospitalize a severe asthmatic. In instances where both the patient and parent are anxious and apprehensive, mild sedation is indicated. It is my own belief that occasionally sedation for the parents is more helpful, especially if it is felt unwise to separate parent from the child. One of the barbiturates is usually adequate, and the most frequently used are phenobarbital ¼-½ grain, pentobarbital (Nembutal), or secobarbital (Seconal) ½-1 grain. Chloral hydrate (3 to 10 grain) is less of a respiratory depressant and very useful, as is paraldehyde (2-8 cc.), and both are effective orally and rectally. Occasionally ether (3-10 cc. in 2/3 to 1 oz. of olive oil) rectally is necessary, and will give one to three hours of relaxation and rest when needed. In some instances meprobamate (Equanil, the new tranquilizing drug) in dosage of 100-200 mg. t. i. d. may be tried.

11. *Oxygen.*—Oxygen is seldom necessary in the acute attack unless there is cyanosis; but it can be tried to see if the respiratory rate is decreased, or when there is evident clinical and/or psychological aid. A tent or

Batson box is used for children—since even the temporary use of a mask may be very frightening to them.

Routine Orders—Acute Asthma

1. Bed rest	preferably air filtered, allergy free room; ? hospital, ? fan
2. Fluids	high carbohydrate, and urge (dehydration is usually present in severe asthma); if vomiting occurs (which is common), parenterally
3. Enema	if needed (or mild laxative)
4. Reassurance	both patient and parents
5. Drugs	(A) sympathomimetics (B) bronchodilators, and (C) expectorants
6. Antibiotics	only when infections present
7. Gamma Globulin	only in infections
8. Bronchoscopy	
9. Hormones	(corticotropin, hydrocortisone, cortisone, prednisone, prednisolone)
10. Sedatives	
11. Oxygen	only for cyanosis and not routinely, since it is an antiexpectorant and when given should be accompanied by humidification

Summary

The routine treatment of uncomplicated asthma with drugs in children is fairly standard and should be common knowledge with all physicians. In definite and proved infectious asthma, antibiotics are indicated and are at times useful in prevention and prophylaxis—similar to their use in rheumatic fever. In some persistent and recurrent upper respiratory infections, gamma globulin is indicated and effective (every three-four weeks). The hormonal drugs should be reserved for cases not responding to routine and ordinary medication. Careful follow-up and complete allergic management after the attack are always needed, since most children do not tend to "outgrow their asthma."

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The Development and Management of Intractable Asthma of Childhood

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Control of childhood asthma can be achieved in approximately 90% of the patients who are presented for treatment. These results transcend those obtained in the therapy of most other chronic diseases. Yet, for the practitioner the intractable asthmatic children who comprise the remaining 10% present a most difficult medicosociopsychological problem. Because of the relatively high incidence of asthma in the United States, the parents of these children compose a substantial group of people who are often voluble and vociferous in condemnation of the failure of the established methods of therapy as they pertain to their child. Their discouragement becomes infectious and has been known to halt other parents from continuing to seek help for a child until emphysema and fibrosis has supervened. Such a child readily falls a prey to quack nostrums and/or wanders about the country in search of the "magic climate" or the "magic pill."

As a result of a plea by Peshkin in 1930,[1] a definitive program for the care and rehabilitation of these childhood intractable asthmatics was established and supervised by him in 1940 at the Jewish National Home for Asthmatic Children at Denver. Much has been learned about the make-up of these children in the ensuing years. Our experience in the management of these patients enables us to postulate the etiologic factors involved in the development of intractability as well as to promulgate the elements of therapy necessary in these cases. These, then, are the frames of reference for this paper.

The Webster definition of intractability is "not easily managed, directed or controlled." Asthma in general is rarely easily managed, yet the proper application of desensitization therapy in addition to the symptomatic or medicinal approach produces a high percentage of control. Ferreting out the multitudinous causes of allergic manifestations is often a detailed and time-consuming procedure. In this respect, then, all asthma might be considered intractable. Obviously, this is not the case. Peshkin,* therefore, defined intractability in asthma as a severe, perennial condition, unresponsive to allergy therapy as well as the usual types of medicinal therapy. Allergy therapy must have been continued for at least one year following a thorough allergy survey before the patient is deemed intractable. We arbitrarily include those patients who are partially or temporarily controlled only by steroid drugs as intractable asthmatics, since we believe such therapy is not definitive and besides falls outside of the realm of easy management. Almost all of the patients referred to in this report were admitted to the institution only if the criteria for intractable asthma were fulfilled.

The most startling observation arising from the admission of more than 500 children to the institution between the ages of 5 and 16 years since the program began is the response to the institutionalization approach. Fifty per cent of these children were free from asthma upon or within a few days after admission and had no further asthma during their stay. In another 30%,

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* Reference 2, page 54.

we noted progressive lessening of asthma during the first year and freedom from asthma during the second and last year of residence. An additional 10% "lost" their asthma upon admission, but the condition recurred during the pollen season. In still another 5% of the patients, asthma continued unchanged but did not interfere with most of the usual activities. The remaining 5% continued to have asthma, unaffected by institutionalization, and two children of this group died while in the Home.

Consideration of the reasons for this excellent relief from asthma involves three principal areas. The matter of climate is foremost in the minds of those parents whose children were admitted from areas which were described as humid, cold, or changeable. Some physicians postulated that relative freedom from respiratory infection and lack of exposure to allergens, irritant smokes and dust explained the results obtained. Peshkin developed a theory † that improvement at Denver was mediated by separation of the child from an environmental emotional overload, and coined the term "parentectomy" to emphasize the principal factor involved in this procedure.

Climate as a significant factor in the total result was ruled out by the simple expedient of admission of seven children from the immediate area of Denver and 24 children from areas within the Rocky Mountain region where the climate is quite similar to that of Denver. These children did as well as those from more remote areas. This confirms the initial report by Peshkin.[1] Thus, climate itself is not of great importance.

It is true that we eliminated obvious inhalant allergens, such as feathers, danders, and mattress and rug dust, but it is equally true that these measures failed when the child was in his own environment. The majority of the patients were encouraged to eat a full diet and tolerated this regimen. A small group of children evidenced symptoms, especially those who were markedly sensitive to egg, fish, or nuts. In the latter instances urticaria rather than asthma ensued when the offending food was ingested. The Denver atmosphere has much mold and some of the same pollens as in the areas from which the children came. The weed pollen seasons are longer and less predictable than many other geographical areas. Thus, the results could not be ascribed to allergen avoidance.

Respiratory infection is equally and sometimes more prevalent in the institution than in the child's own environment, and relatively only infrequently leads to asthma under these circumstances.

The critical role of the emotional overload in the production of intractability was suspected by Peshkin soon after the beginning of the program. Then evidence began to accumulate along with experience and particularly with the unique and unparalleled opportunity to observe these children 24 hours a day and 7 days a week for 2 years or more.

This procedure has demonstrated that tensions produced by separation of the child from his own environment and transportation to a new environment are different from those present in his own setting. Thus, asthma subsides or improves. When such a child begins to wheeze when his parents merely advise him of their forthcoming visit to Denver or when they actually arrive on the Denver scene one year later, the conclution seems inescapable that his relationship to his parents or his environment represented by the parents played the dominant role in the continuation of the former state of asthma. Additional observations which confirm this conclusion include flare-up of asthma just prior to the child's departure from Denver to his own home and asthma when adult personnel at the Home inadvertently become panicky or upset by behavioral problems or minor coughs and coids. Situational episodes producing asthma in his own home produce asthma within the institution. Analysis of the type of environment provided at Denver shows that separation to

† Reference 2, page 39.

Denver controls asthma mainly by freedom from overprotective and overanxious parents. Other factors considered important in improvement are permissive atmosphere of the Home allowing the child to express himself through talk and play without fear of reprisal and psychotherapy adjusted to the child's age level.

Examination of histories of children admitted in the light of psychiatric evaluation during their stay in the institution reveals a pattern of progression of asthma from the seasonal or nonseasonal sporadic type to the perennial type with seasonal aggravation or sporadic increase associated with infection. Reference to disturbed relationships within the family constellation appeared in the histories usually at about the time asthma became perennial. A composite story of the manner in which the emotional influence affected the course of the disease and produced intractability was constructed from these histories. Such a story begins with the early attacks of asthma which frighten both the child and the family. As long as relief is obtained by antiallergic management, the cycle is repeatedly broken and panic and fear are less important. The first time that drugs are slow in giving relief is the first time fear and panic become dominant. The inability to breathe properly is upsetting to all and especially to a child, since attention is not normally drawn to the usually involuntary respiratory function. Fear is always accompanied by anxiety, which aggravates asthma. Thus we see the disease itself develop into a vicious cycle of asthma, fear, anxiety, panic, and finally more asthma. Soon the family life begins to center about this chronically ill child. Consciously or unconsciously, the parents resent this intrusion. They feel guilty about their resentment and intensify the attention paid to the child. The child soon realizes that asthma means attention, more attention and love than when he was not so ill or when he was well. The child realizes that asthma has its uses. As asthma increases the parents restrict the child's activities more and more and draw the child more to a cloistered existence within the family. Family quarrels and marital problems which may not have been noticeable before become magnified in the eyes of the child. Neurotic tendencies of the parents are brought out under these circumstances. The child reacts with more asthma to this new life situation. It is small wonder that hyposensitization injections induce no positive effect in situations of this type. This briefly characterized the intractable asthmatic child—the type of child admitted to the Home.

Further knowledge of the emotional problems in the environment from the child's viewpoint has been obtained by the administration of a battery of psychological tests to the last 100 consecutive children admitted to the Home. The psychometric tests were composed of the Wechsler-Intelligence Scale for Children, Rohrschach, Thematic Apperception, Machover Draw-A-Person, and Bender-Gestalt tests. The WISC, an intelligence test for children, showed a normal distribution curve for test scores, with the majority falling within the normal range. There were a few very low and a few very high scores. However, this group of intractable asthmatic children is not at all superior in intelligence over other groups of children. These findings also negate the popular notion that allergic children are an intellectually superior group.

Projective psychological tests, the remainder of those previously mentioned, revealed that this group predominantly differs from the average normal in the emotional content of their responses. The personality traits common to most all of the group were marked immaturity, anxiety about the body, and poor relationships with people in general, especially parental figures. In other respects, the presenting pathology varied widely. A substantial number of the group manifested neurotic behavior by acting out their conflicts. An equal number, however, were withdrawn. Two children were considered prepsychotic and one child

actually psychotic of the juvenile schizophrenic type.

It seems clear that these intractable asthmatic children have emotional problems which revolve about the home situation. When separated from this environment, asthma either disappears or improves in a large percentage of cases.

The Rehabilitation Program conducted at the Home now has enough evidence in its favor to establish it as indicated and practical procedure in the management of intractable asthma of childhood. The primary aim of therapy is to cause a break in the vicious circle of asthma. Separation from the home environment, parentectomy, can accomplish this in these cases. Unfortunately, institutions dedicated solely to the care of these children are available for only a small number of the estimated cases of intractable asthma in this country. Therefore, the home town facilities which are available must be modified by the attending physician to accomplish the results of separation. More frequent admission to the hospital for more prolonged periods of time should be encouraged as long as it is feasible to sharply limit parents' visitation. Convalescent homes for children are becoming available in many parts of the country and may serve to practice separation for longer periods than the general hospital. The homes of relatives or friends providing a warm emotional climate will often suffice to successfully separate a child from his own environment, especially if located some distance away. This implies not exposing the child to persons who represent an extension of the conflicts present in his own home. If the family has the means, summer camp and boarding school provide separation and limited visitation. Excellent results are often obtained if the personnel of such establishments are apprised of the needs of these children and are guided in their management. Foster homes can also be successfully used for purposes of separation.

Parentectomy is the first step toward rehabilitation. The second step is family counselling for those left behind, notably the parents. Experience at Denver has shown that relapse upon return home may occur in those cases where the environment remains emotionally unchanged. Family service associations and mental hygiene clinics often are willing to undertake this program even for the private patients of practicing physicians. Psychological testing of both the child and his parents can provide a guide to the direction of counselling which can be performed by practitioners when organized programs cannot meet the need.

Widespread use of the procedure of separation and the counselling of parents in the emotional component of asthma and its management may aid in reduction of the number of childhood intractable asthmatics now present in our population and of the morbidity from this disease in adolescence and early adulthood.

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Accidental Transanal Perforation of the Rectum

An Obscure Cause of Peritonitis in Infancy and Childhood

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Over the past few years three cases of transanal perforation of the rectum in childhood have been brought to our attention. Two of these cases succumbed, with the lack of diagnosis both before and during surgery of prime importance. So obscure were the sites of perforation (even at autopsy) in all of these cases that it seemed expedient to emphasize this type accident and to suggest diagnostic maneuvers that might prove helpful during an otherwise frustrating exploratory operation.

Report of Cases*

CASE 1.—Two-day-old girl. Admitted Aug. 13, 1953; died Aug. 14, 1953. History: At end of a normal first day of life this 2270-gm. (5-lb.) baby was found in "shock," with evidence of bilious vomiting. Meconium stools had been passed. Physical examination revealed a critically ill cyanotic infant with a distended quiet abdomen. X-rays showed air under the diaphragm. Treatment: I. V. and antibiotic therapy was followed by an unrewarding laparotomy, which disclosed a feculent type of peritonitis without obvious etiology. Death ensued 15 hours later. Autopsy showed a 0.3×0.5 cm. left-rectal-wall perforation at the level of the peritoneal reflection. Histological examination of the area of perforation revealed minimal nonspecific inflammation.

CASE 2.—A 2 9/12-year-old girl. Admitted May 31, 1955; died June 2, 1955. History: Seven days of abdominal pain, vomiting, and diarrhea followed by apathy and prostration was related by the father. Physical examination showed overwhelming peritonitis with no localizing findings. X-rays of chest and abdomen were of no help. Treatment: Vigorous I. V. and antibiotic therapy was followed by a brief but unsuccessful abdominal exploration, characterized by an extensive foul-smelling peritonitis that spelled a visceral perforation that defied detection. The patient died on the first postoperative day of overwhelming sepsis. Autopsy showed a large anterior rectal wall perforation at the level of the peritoneal reflection (Fig. 1). Histological examination of perforated area showed nonspecific inflammation.

CASE 3.—A 10-year-old boy. Admitted Oct. 29, 1955; discharged Nov. 6, 1955. History: The patient fell from his bunk bed onto the barrel of a rifle which tore his rectum—he was rushed to hospital. Physical examination revealed a well boy with a diffusely tender abdomen. Rectal examination revealed a torn sphincher mechanism on the left with prolapsing small bowel. X-rays of the abdomen were noncontributory. Treatment: Exploratory laparotomy revealed a perforation of the rectum at the level of peritoneal reflection. This perforation was closed primarily. A contused laceration in the small bowel was resected and end-to-end anastomosis performed. Hospital course and follow-up were entirely favorable.

Mechanism of Perforation

It is implied, though certain in only Case 3, that all of these children had accidental transanal perforations of the rectum. In Case 1, the infant, a thermometer might be implicated; Case 2, a toy with a stick-like projection (viz., Tinkertoy) may have become a weapon by a routine tumble (Fig. 1), and in Case 3, the rifle barrel can be visualized as the agent of perforation when

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* Case 1, Milwaukee Children's Hospital (private patient of Drs. E. Epstein and S. Sakaguchi); Cases 2 and 3, Milwaukee County Hospital.

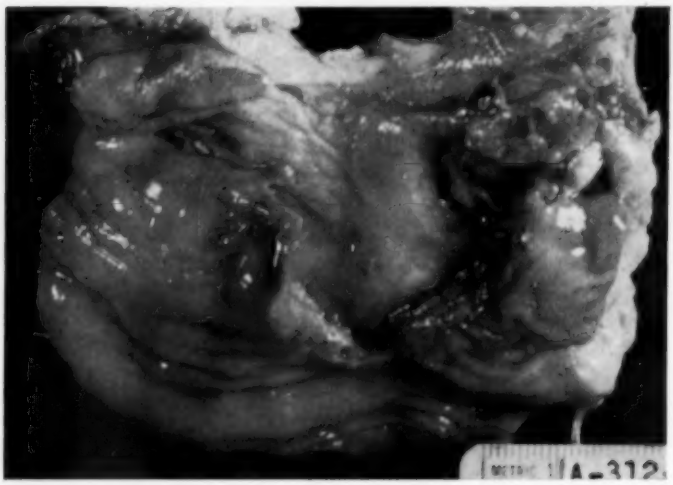
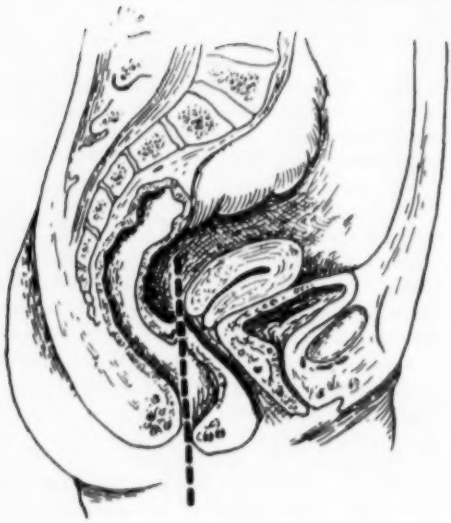


Fig. 1.—A large rent in the rectum is shown with the anal canal below. The uterus is seen through the perforation.



Transanal Perforation of Rectum

Fig. 2.—The mechanism and constant position of accidental transanal perforation of the rectum is clearly shown.

the boy fell from his bunk bed. Figure 2 indicates the route of the "attack" and the fairly constant position of the defect.

Diagnosis

Because preschool children (those most accident prone) find it hard to express the serious nature of such an injury, early diagnosis is perhaps beyond our reach. Even at an older age the injured child may be hesitant to describe such an accident, just as a man with a ruptured sigmoid colon is shy to discuss a friendly trick with a compressed air hose. Pelvic peritonitis is a teacherous entity in adults and may be just as stealthy in childhood (viz., Case 2). One's, index of suspicion, mother's, dad's, and doctor's alike, must be high when abdominal pain and even the vaguest hint of perineal trauma, with or without some rectal bleeding, center on an acutely ill child with developing peritonitis. In infancy an awareness of its occurrence would seem to exhaust clinical diagnostic aids. It should be emphasized that a negative rectal examination does not rule this entity out. An upright x-ray of the abdomen may disclose free air but only confirms the clinical impression of a catastrophe without localizing it.

Detecting the cause of peritonitis at laparotomy is still another problem. Only a certain number of entities are repeatedly brought to the surgeon's attention, so that missing this inapparent lesion of our discussion is perhaps understandable. In reviewing 270 cases of peritonitis from infancy to 15 years of age at Milwaukee County and Milwaukee Children's Hospi-

tals, occurring since 1940, the following table of incidence seems worth emphasizing as shown (Table).

It may be surmised from this table that the cause of peritonitis either before or during operation in childhood is usually obvious, save for those "primary" in nature and those due to obscure trauma. "Primarily" (hematogenous) peritonitis almost without exception afflicts the child ill with nephrosis, pneumonia, or some other debilitating disease. If an operation is deemed advisable in these cases a nonfeculent exudate is encountered, and on Gram-stained smear cocci rather than Escherichia coli type organisms are found. On the other hand, in cases with visceral perforation induced with deception from below (rectum) or from above (gastric rents especially in the newborn),[1] the surgeon is confronted with a foul-smelling peritonitis arising in an otherwise well child—the site of leakage can be readily anticipated but not located!

In cases 1 and 2 visceral perforation was strongly suspected during the operation, and the following maneuvers in retrospect might have been diagnostic. As previously mentioned, all of these rents occurred in a fairly constant position (Fig. 2):

A. Palpation in the cul-de-sac should disclose an opening when produced by larger blunt objects, and

B. Rectal insufflation with the pelvis submerged in saline might identify a tiny site of leakage, much as one detects a small hole in an inner tube.

Recently we had a chance to try the latter maneuver (B) when an 8-year old boy was admitted to the Milwaukee County Hospital, having been hit in the right buttock and perineum by a close-up blast of a 12-gauge shotgun while lying in bed. He subsequently developed peritonitis, and gentle proctoscopy revealed a questionable site of perforation at the 6-in. level. At laparotomy multiple small-bowel perforations were closed, and a hole in the posterior peritoneum was detected at the sacral prominence. A perforation in the rectosigmoid was not apparent, but this was confirmed with greater assurance by careful rectosigmoid insufflation via a Foley catheter, as suggested previously. No form of peritoneal or perirectal drainage was deemed necessary. The boy made an uneventful recovery.

Treatment

All of these rectal rents, if operated on with reasonable urgency, should lend themselves to primary closure. Proximal colostomy may at times be advisable in lesions where inflammation and necrosis cast doubt on the closure holding up.† In Case 3 primary closure of the rectum was readily performed and effective. Lest some decide that conservative management of a rectal tear might suffice, this latter case involving both large and small bowel should serve as a good warning—even blunt transperitoneal trauma demands a thorough exploration. The insidiousness of this type lesion also casts some doubt on the expectant treatment of any ill-defined peritonitis (viz., Case 2).

Conclusions

The differential diagnosis of peritonitis in childhood is a rather limited one. Accidental transanal perforation of the rectum is such an infrequent and obscure cause that it may be overlooked.

Three cases of this entity, from the newborn period to 10 years of age, are presented to place this serious lesion on record. To our knowledge this subject has not been presented in the literature previously. Even a trifling perineal injury followed by abdominal distress, with or without rectal bleeding, should bring this lesion to mind.

Preoperative diagnosis in the absence of a reliable history may be impossible. X-ray evidence of free peritoneal air merely confirms the need for urgent exploration.

At laparotomy, especially where fecal contamination is evident and no lesion is

† References 2, 3, and 4.

found on routine manipulation of the bowel, two maneuvers should be employed: (1) Cul-de-sac palpation; (2) rectal insufflation with the pelvis filled with saline.

Primary closure of the rent would seem to be the treatment of choice, though proximal colostomy may be a necessary addition in neglected cases.

Summary

1. Three cases of accidental transanal perforation of the rectum are discussed.

2. A method for its detection at laparotomy is presented.

3. Surgical intervention for cases of obscure peritonitis in childhood is recommended.

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Ichthyosis Congenita

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Much has been written but little settled regarding the subject of newborn infants encased in a sheath-like membrane (Fig. 1). This collodion- or parchment-like covering is so typical in appearance that even though one has not seen this condition previously, he will use these terms to describe the infant. Shortly after birth this sheath dries, fissures, and tends to separate from the body in sheets.

In 1895, Grass and Török [1] introduced the very descriptive term "lamellar exfoliation of the newborn" and suggested that this was an entity apart from ichthyosis congenita (harlequin fetus). Five years later, Riecke [2] classified a group of 54 infants and children into three types of ichthyosis congenita. The first group was that of the harlequin fetus, which invariably dies. The second group consisted of the infant born with a collodion-like sheath, in whom death may occur. The third group has minimal findings at birth, or shortly thereafter, and lives. The second large grouping in this classification certainly has much in common with the patient of Grass and Török.

Since 1900, a new terminology has been suggested by Hess and Schultz,[3] but the fundamental grouping of Riecke still appears valid. As recently as 1947, Civatte [4] wrote that "lamellar scaling of the newborn hardly merits the term of dermatosis."

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Fig. 1.—Ichthyosis congenita with parchment-like skin.

However, eight years later Shelmire Jr.[5] suggested the acceptance of the concept of "lamellar exfoliation of the newborn" as a primary disease with three subtypes.

We present the following six cases of ichthyosis congenita to show some of the variations of this condition, its familial nature, and the transition into frank ichthyosis of the skin of the infant that survives.

Report of Cases

Case 1.—A 40-hour-old full-term white boy was admitted to the Children's Memorial Hospital on March 18, 1955, and died on March 22, 1955. He was admitted because of an abnormal skin that was present at birth plus other congenital defects. The family and obstetrical history was noncontributory. The mother's serology test for syphilis was negative.

At birth there was a marked edema and the infant seemed to be encased in a collodion-like skin. He assumed the fetal position and seemed to be held thus by the taut skin. The skin was tight and edematous over the hands and feet, and it wrinkled when touched. In some areas, especially the groin, axillae, and perineum, the skin was red, fissured, and denuded. The mucous membrane of the mouth sloughed spontaneously.

This infant also had a purulent discharge from the eyes, syndactilism of the fourth and fifth digits of the fingers and toes, and a grade II, apical systolic murmur. The femoral pulsations were absent. The testes were not palpated in the scrotum. No laboratory data was obtained.

Therapy consisted of incubator care, oxygen, parenteral fluids, cortisone, and an aqueous solution of 1% gentian violet to the oral lesions.

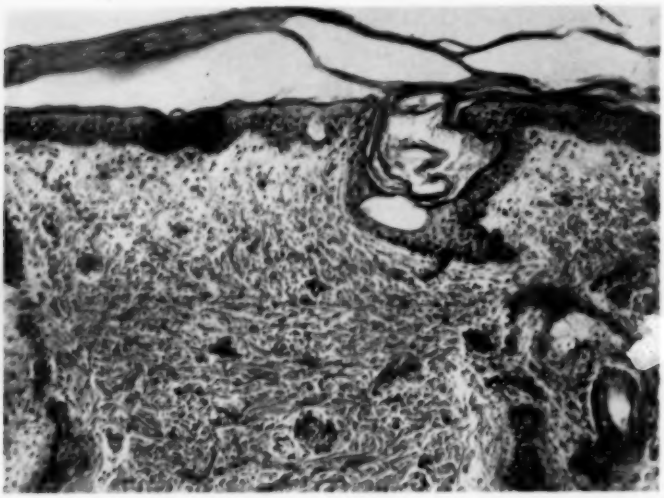

Fig. 2.—Photomicrograph of skin of patient with ichthyosis congenita.

Pertinent autopsy findings were (1) lamellar exfoliation of the skin and (2) congenital heart disease consisting of a patent foramen ovale, interventricular septal defect, infantile coarctation of the aorta, and a patent ductus arteriosus. Other findings consisted of congestion and edema of the thoracic and abdominal viscera, uric acid infarcts of the kidneys, bilateral abdominal testes, bilateral adrenal cortical hemorrhage, bilobar right lung, accessory spleen, Meckel's diverticulum, bilateral atelectasis of the lungs, and syndactilism.

Microscopic examination of the undenuded skin (Fig. 2) showed the outer sheath to be composed of a thick stratum corneum with marked parakeratosis. This sheath was largely split away from the deeper structures, the cleavage plane being through the deepest layer of keratotic cells. Keratotic plugs were present in the orifices of the glands. The remaining epidermis had a narrow layer of partially cornified cells, many of which contained nuclei. Beneath this the basal layer and the stratum Malpighi appeared intact. The dermis was apparently spared.

The denuded skin areas had practically no epidermis. The cellular linings of the sebaceous glands, hair follicles, and sweat glands were apparently normal, but keratotic plugs were present in these orifices. In areas in which the dermis was exposed, the superficial portions were uniformly eosinophilic with a loss of staining differential. In the deeper portions there was a slight infiltration of lymphocytes, macrophages, and occasionally polymorphonuclear leukocytes. These inflammatory cells were more numerous about blood vessels. Similar cells appeared in scattered areas in the subcutaneous fat layer.

Case 2.—A 4-hour-old full-term white boy was admitted to the Children's Memorial Hospital on April 20, 1955, because of skin lesions which were present at birth. The family and obstetrical history was noncontributory. The mother's serologic test for syphilis was negative.

With the exception of the congenital defects of Case 1, the appearance of these two infants was identical. Treatment consisted of incubator care and liquid petrolatum (mineral oil) to the skin. The following day death occurred as the baby was being fed. Permission for an autopsy could not be obtained.

Case 3.—A full-term Puerto Rican girl (Fig. 3) was born Sept. 30, 1954, with a skin that simulated parchment encasing her entire body. She was the product of an uneventful fourth pregnancy. No siblings had ever been so afflicted. Extensive scaling of the skin started soon after birth, and she required hospitalization for the first two months of life. In the pediatric and dermatology clinics at the Research and Educational Hospital it was noted that her physical and mental development was normal. However, the scaling of the skin had persisted. Now at the age of 2 years this child has a generalized ichthyosis with varying degrees of erythema. This redness seems most intense during the cooler months of the year which is the time that the ichthyosis is most pronounced.

Case 4.—A full-term boy sibling of Case 3 was born Aug. 12, 1955, died on Aug. 17, 1955. He was the product of the mother's fifth pregnancy, which had been uneventful. The appearance of this infant was identical with that of the sister who lived. Postmortem findings were unremarkable except for those of the skin, which were described in Case 1.

Fig. 3.—Ichthyosis congenita eventuating into typical extensive ichthyosis.

Case 5.—A Negro girl was born at the Research and Educational Hospital on Dec. 27, 1952. She was the product of an uneventful, full-term, first pregnancy. At the time of delivery a parchment-like skin was noted with a generalized edema.

In addition, the infant had a bilateral ectropion, the ears appeared shortened, and the upper part of the ear was pointed. The mouth seemed to be held taut by the stress of the skin. At the age of 3 days the skin which had been so tense began to split. The underlying denuded skin was red. When 3 weeks old she was able to leave the hospital with only an unusually dry skin to show for her experience. However, at 6 months of age her skin resembled that of a typical ichthyosis patient. Her mental and physical development is otherwise normal.

Case 6.—A full-term girl sibling of the above was the product of an uneventful, third pregnancy. The mother's second pregnancy produced a normal girl. The appearance of the third baby was identical with that of Case 5. Seven days after birth the patient died. Pertinent postmortem findings were a confluent suppurative pneumonia with abscesses containing Staphylococcus aureus, visceral congestion, petechiae of the epicardium and pleura, and the typical sheet-like exfoliation of the skin common to all of the newborns described above. Microscopic examination showed the epidermis to be slightly atrophic, and the stratum granulosum was thin. Keratotic plugs were present as in Case 1.

The mother of patients 5 and 6 has received numerous courses of penicillin therapy for syphilis. Her children are free of this disease as evidenced by negative roentgenograms of their long bones and negative serologies. These studies were done at birth, and at later intervals. As an added precaution her first infant was given a prophylactic course of penicillin as an antiluetic therapy. This had no effect on the skin. The second infant died before a similar program could be instituted.

Comment

A review of the literature shows that most cases of ichthyosis congenita tend to be sporadic. If the infant survives, the skin progresses to ichthyosis of varying degree. Specific cases of familial involvement, as shown in our series and in the literature, leaves little doubt that this can be an inherited trait of the recessive type.

Clark's [6] report on the incidence of this disease in a family substantiates the above. The patient he observed was a full-term girl born with a membrane resembling cellophane. The covering of the skin was loosely attached, and exfoliated during the first week of life. The remaining skin was dry and red. At the age of 2 months ichthyosis developed and was still present 6 years later at the time of his report. This patient was one of 12 children, and she had a brother and a sister who were born with the same type of skin but did not survive. Of interest is that the maternal grandmother had 16 children, of whom two boys and a girl had ichthyosis.

Some have tried to explain the cause of this collodion-like covering of the newborn by attributing it to prematurity, or to the retention of a fetal membrane.[7] On a statistical basis alone one can dispense with prematurity as being a factor. The epitrichial layer theory has several weak points. If the membrane was laid down and was to be exfoliated by the seventh month of fetal life, how can one explain the progression of the pathologic state and the continuation of ichthyosis for an indefinite period? The persistence of the epitrichial layer is a the-

oretical state advanced by findings in lower animals. As far as we can determine the existence of such a covering of the human fetus seems to be based solely on inference.

Grouping these cases as "lamellar exfoliation of the newborn" is emphasizing a clinical appearance rather than a concept of disease. In dermatology many cases may be described as having lamellar exfoliation and yet have nothing in common with each other or with ichthyosis congenita.

Summary

Six cases of ichthyosis congenita are presented.

Evidence has been offered to show the familial tendency of this condition. It is an inherited trait of the recessive type.

Riecke's original grouping of the three types of ichthyosis congenita is still valid.

The progression of ichthyosis congenita with lamellar exfoliation of the skin into permanent ichthyotic skin has been described.

25 E. Washington St.

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Studies in Hyperbilirubinemia

I. Hyperbilirubinemia of the Newborn Unrelated to Isoimmunization

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With the development of increasingly precise criteria for the various types of hemolytic disease and of hepatic disease, the role of these disorders in the causation of neonatal jaundice has become greatly clarified. By the same token, it has become possible to delineate a residual group of hyperbilirubinemias in the newborn period, the cause and mechanism of which still remain obscure. This study is designed to call attention to the problems presented by this group because it is pertinent to the definition of physiologic jaundice and because of the probable relationship of hyperbilirubinemia to kernicterus.

This report concerns 50 patients, about half of them full-term infants, seen in a pediatric hospital during a period of nine months, who had bilirubinemia significantly in excess of levels currently considered normal for "physiologic" jaundice and who came to our attention because of early or excessive clinical jaundice or both. Only those infants were included whose major blood groups were compatible with those of the mother and in whom no effects of isoimmunization of any kind could be demonstrated by currently available methods. We have reason to believe that a number of babies who were products of heterospecific pregnancy had the same condition, but we deliberately excluded them to eliminate any possible influence of isoimmunization.

In the absence of isoimmunization or evidence of liver disease, it would appear that excessive hyperbilirubinemia in the newborn may be due to the same unknown mechanism as that responsible for physiologic jaundice —but here we are first confronted with the question, what is physiologic jaundice? What quantitative limits might be considered as established?

It has long been recognized that at least 50% of newborn infants may show detectable jaundice and that even in cases without jaundice there is a rise of the serum bilirubin level. The range of this rise has been studied by many. In the series of Hsia, Allen, Diamond, and Gellis (1953),[1] Zuelzer and Kaplan (1954),[2] and Obrinsky (1954),[3] a bilirubin level of 12 mg. per 100 cc. was only rarely exceeded in the normal full-term infant. We therefore arbitrarily chose to study those full-term infants who had levels above 12 mg. per 100 cc.

It is even more difficult to know what level of serum bilirubin should be considered within the physiologic range for the premature infant. It is generally recognized that bilirubinemia is greater in this group than in the full-term baby. According to some authors, the peak is reached later in this

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group. In Hsia's series (1953) and also that of Obrinsky (1954), the mean maximum bilirubin level did not exceed 12 mg. per 100 cc., although there were some individual infants whose level exceeded 15 mg. per 100 cc. We are aware that higher mean maximum levels have been found in a more recent series,[4] but we chose to investigate premature infants whose bilirubin exceeded 15 mg. per 100 cc.

Another criterion widely used for the definition of physiologic jaundice has been the time of onset. It seems agreed today that jaundice on the first day is "unphysiologic" and usually indicates hemolytic disease. More precisely, levels of bilirubin exceeding 10 mg. per 100 cc. within the first 24 hours are regarded as abnormal.[5] In Hsia's group, only one full-term and one premature infant exceeded this level. In Obrinsky's series, no infant reached this level. For this reason we studied any infant, full-term or premature, whose bilirubin reached a level of 10 mg. per 100 cc. on the first day.

Observations

It was not to be expected that the group selected on the basis of these criteria would prove to be homogeneous. Three of the fifty patients proved to have congenital hemolytic anemias. In one of these the diagnosis of congenital spherocytosis could be made on the first day. In two others the diagnosis of congenital nonspherocytic hemolytic anemia was ultimately established. These three patients whose illness clinically simulated hemolytic disease of the newborn will be excluded from the further discussion because the element of increased hemolysis, albeit unrelated to isoimmunization, distinguished them from the remainder of the groups. Similarly the case of a fourth infant who was found to have a large congenital cyst involving the entire right lobe of the liver as well as hepatitis, diagnosed by laparotomy and biopsy, is excluded. In the remaining 46 cases with hyperbilirubinemia no primary disease could be found, and the following discussion is concerned only with these.

Twenty-four of this group were full-term (by weight); twenty-two were premature. Twenty-eight were boys; eighteen were girls. Thirty-two were white; fourteen were Negro. The maximum bilrubin values in the full-term group ranged from 11.8 mg. per 100 cc. (on the first day) to 32.2 mg. per 100 cc. Serum bilirubin values in these infants are charted in Table 1. Eight of the twenty-four full-term infants had bilirubin levels greater than 20 mg. per 100 cc. some-

TABLE 1.—*Daily Bilirubin Levels (Milligrams per One Hundred Cubic Centimeters) in Full-Term Infants with Hyperbilirubinemia*

Patient	Weight, Gm.	Day 1	2	3	4	5	6	7	8	Type Mother	Baby
1	3100					19.6	16.6	14.4	8.1	O N CDe	O N CDe
2	2500				24.0	28.0*	18.8	21.8	20.0	A$_1$ MN CDE	A$_2$ cDE
3	2950			15.7	16.2	17.5	18.0	14.0		O MN CDe	O N cDE
4	2700		19.0	17.4	12.6	7.0				O N cde	O N cDe
5	3430		11.0	12.7	13.4	9.4	5.0			O MN CDe	O MN CDe
6	2870				30.8*	19.3	16.8	32.2*	13.7	A$_1$ N cDe	A$_1$ MN CDe
7	2870		18.5	18.2	13.8	13.4				O MN cDe	O MN cDe
8	2890		21.6	24.5	20.8	23.5	22.5	18.2		A$_1$ MN cDe	A$_1$ MN cDe
9	4900			28.0*	21.8	18.0	9.8			A$_1$B MN cDE	A$_1$ MN cde
10	3230	12.2	14.2	15.8	16.6	7.3				O MN cDE	O N cDE
11	3600				15.0	16.1	5.9			A$_1$ MN CDe	A$_2$ N CDE/ce
12	2500						15.3	13.0	9.0	B MN cde	O MN cde
13	3150				14.0	16.2	11.7			O M CDe	O M CDe
14	3180				15.7	17.7	19.3	14.0		A$_1$ MN CDe	O MN CDE
15	2930				21.4	19.6	9.6	9.6	3.6	O MN CDE	O M CDe
16	4110	3.0		16.4		20.3		14.4		A$_1$ MN cde	A$_1$ M cde
17	4360		16.8	17.2	13.6	9.8	8.6			A$_2$ MN CDe/c	O N cde
18	3600	11.8	9.8	10.8	1.1					O MN cDe	O N CDE/c
19	4050			27.4	32.2*	26.4		22.7	19.8	O MN cde	O MN cde
20	2500	18.5*	11.9	10.9	10.2					A$_1$B N CDe	A$_1$ N cde
21	2900	11.6	15.7	17.5	22.0	23.0	21.6	19.6	13.18	O MN cde	O N cde
22	2900				23.0*	25.8*	14.6	17.75	14.8	O M CDe	O M cDe
23	3600			14.2	13.5					O N cde	O MN CDe
24	4110			12.2	13.6		18.6	13.7	9.3	O MN CDe	O N cde

* Indicates exchange transfusion.

time during the first week. Six infants had exchange transfusions, and the peak they might ultimately have reached is therefore unknown. Fifteen had levels of 18 mg. per 100 cc. or greater. Only one infant did not have a level of 12 mg. per 100 cc. but was included because the bilirubin rose to 11.8 mg. per 100 cc. on the first day. Figure 1

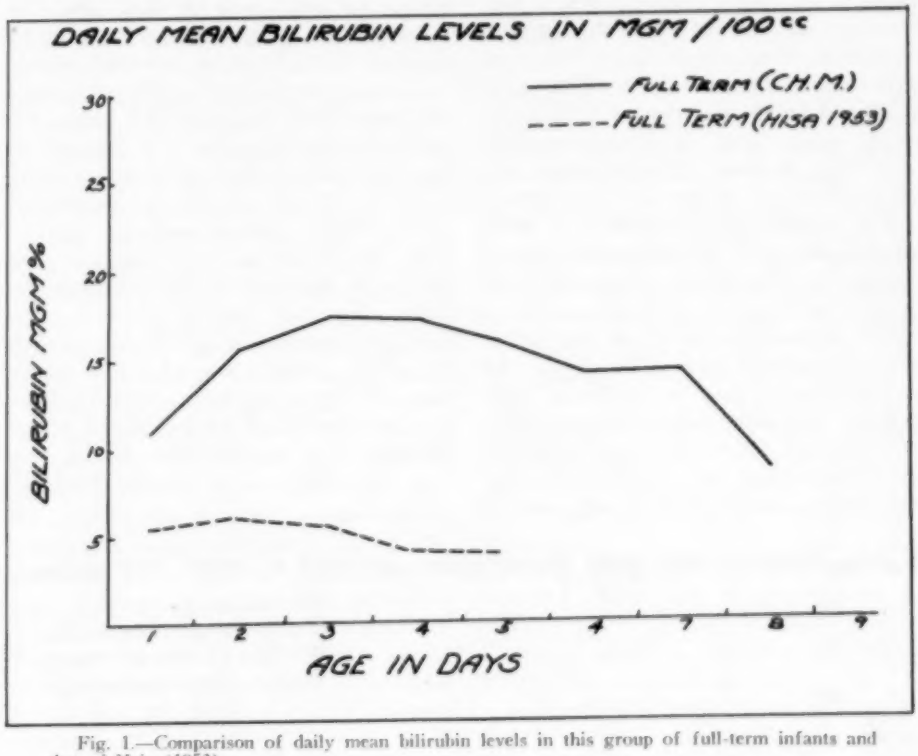

Fig. 1.—Comparison of daily mean bilirubin levels in this group of full-term infants and that of Hsia (1953).

TABLE 2.—*Daily Bilirubin Levels (Milligrams per One Hundred Cubic Centimeters) in Premature Infants with Hyperbilirubinemia*

Patient	Weight, Gm.	Day 1	2	3	4	5	6	7	8	Type: Mother	Type: Baby
1	1790		11.2	16.0	21.2*	14.8	12.6		9.7	A ; MN CDe	A ; N CDE/cu
2	980			14.6	18.5	21.2*	14.2		12.2	A ; MN CDE	O CDE
3	1590						19.3	25.0*	16.5	A ; MN cDE	A ; MN cde
4	1790		12.8	18.0	21.8*	10.2		6.0		B M CDe	O M CDe
5	1470					18.6	17.0	13.7	10.9	O M CDe	O M CDe
6	1620				13.0	15.5	15.7	14.0	14.0	A ; MN cDe	A ; M CDe
7	1080			13.0	17.3	20.6*	19.8	15.7		O MN CDe	O MN CDe
8	1590				28.8*	19.6	20.0	22.4	20.0	AB N CDe	O MN CDe
9	1110		5.45	12.8		16.5	†			O M CDe	O MN CDe
10	1130			11.02	16.6	16.0		12.8		A ; M CDe	A ; MN Cde
11	2440			22.0*	17.6	21.4	21.0	20.8	16.8	A ; MN cde	A ; MN cDE
12	2240			16.6	19.0	24.8	27.0	23.0	15.2	A ; MN CDe	A ; MN CDe
13	1870			21.4*	19.6	20.0	20.0	18.75		A ; MN CDe	A ; MN cde
14	2010		8.2	10.9		20.6	23.6*	16.5	17.0	O MN CDe	O MN CDe
15	2270				31.2	32.0	30.6	†		O MN cDe	O N CDe/c
16	2240	11.2	13.0	6.7	5.8	1.1				A ; B cDE	A ; N cDe
17	2210				20.0*	15.0	14.8	14.0	13.3	O MN CDe	O N CDe
18	1670				18.0	19.6*	14.4	12.6	†	A ; MN CDe	A ; MN CDe
19	2210			12.2	15.8	21.8*	26.2*	11.75		A ; N CDe	A ; N CDe
20	1630			13.3	20.2*	18.0	17.5			B M cDe	B M cDe
21	1620				24.4*	23.8	21.4	20.0	8.3	O cDe	O MN CDe
22	1640			20.6*	12.2	16.2	14.0		11.4	B N cDe	O MN cDe

*Indicates exchange transfusion.
†Indicates infant died.

shows the composite curve of the average daily bilirubin levels in the full-term infants in contrast to the average levels in 24 normal full-term infants from the series of Hsia. There is a tendency toward sustained high levels beyond the third day of life, which is the time of maximum jaundice in most full-term infants. The latter part of the curve is affected by the omission of the post-exchange values. Had no exchange transfusions been done the bilirubin values from the fourth day on might have been higher.

Table 2 shows the distribution of serum bilirubin levels in the premature infants. Among the 22 premature infants the maximum values ranged from 13 mg. per 100 cc. (on the second day) to 32 mg. per 100 cc. Sixteen reached a level of 20 mg. per 100 cc.; fourteen of these had exchange transfusions. One other infant with a level of 19.6 mg. per 100 cc. was also exchanged. Only three infants had levels below 18.5 mg. per 100 cc. One of these did not reach 15 mg. per 100 cc. but was included because the bilirubin was 11.2 mg. per 100 cc. within the first 24 hours. Figure 2 shows the average daily bilirubin levels of these premature infants compared with other groups. The infants in this group displayed an exaggeration of the tendency of premature infants to continue to accumulate bilirubin beyond the second and third day, and, hence, the peak levels in this group were attained on the sixth day. Further accumulation might have been evident had not the majority of these infants received exchange transfusions. While the levels attained are comparable to those seen in erythroblastosis, the peak occurs much later in this series. The curve of accumulation of bilirubin parallels that of other premature and full-term groups until the fourth day, but it seems that there is a prolongation of the inability to excrete bilirubin. The hyperbilirubinemia in each case represented an elevation of "indirect" bilirubin.

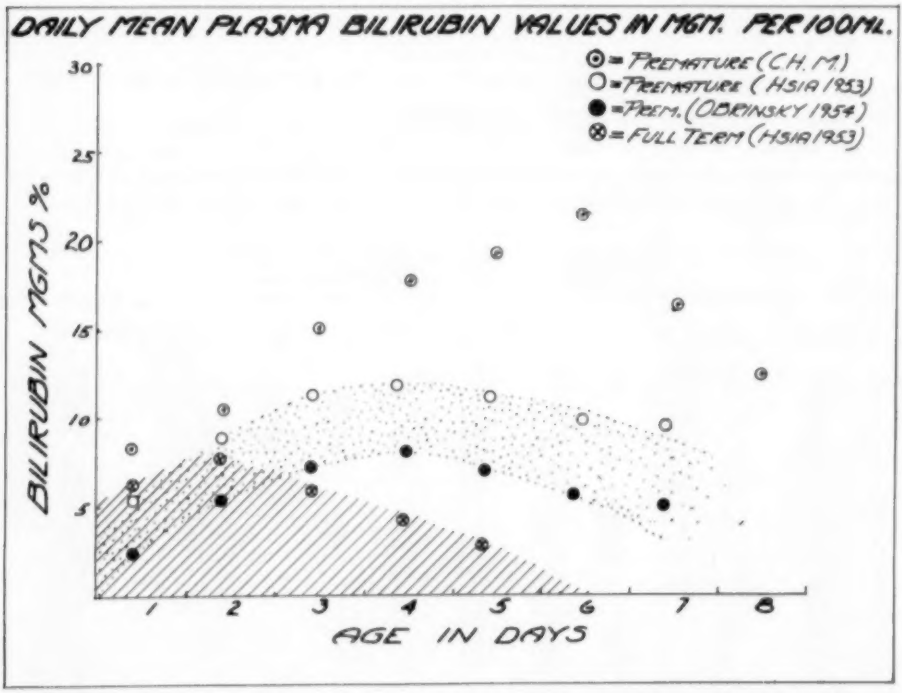

Fig. 2.—Comparison of daily bilirubin levels in this group of prematures with those in other premature and full-term infants.

It will be recalled that these infants appeared to be normal except for hyperbilirubinemia. Therefore an attempt was made to evaluate the possible influence of certain prenatal and paranatal factors on the development of hyperbilirubinemia. The severer cases, those in which the bilirubin reached levels above 20 mg. per 100 cc., were compared with the milder ones within the group, since there were no normal infants for comparison. It was hoped that significant factors would be more apparent in the severely affected group. However, scrutiny of the prenatal and birth histories failed to yield any correlation with such factors as degee of parity, previous transfusion of the mother, or early rupture of the membranes (Table 3). Since all patients were referred from other hospitals, the quality of information concerning duration and other details of labor was too variable to permit an attempt at statistical correlation. The babies' condition on admission did not suggest birth trauma except in one premature infant. Deliveries were described as normal in all but four, and two deliveries were unattended. One delivery was "precipitate." Presentation in all but one was normal. There was some correlation with birth weight, as indicated by the fact that 25% of the 24 full-term infants had bilirubin levels in excess of 20 mg. per 100 cc. as compared with 72% of the 22 premature infants. The fact that there was also a higher incidence of premature separation among the more severely affected infants cannot be evaluated, since it was in itself a causative or contributory factor to prematurity. However, within the premature group a special effect of these hazards was not discernible (Table 3).

The only other finding which was encountered somewhat more frequently in the severe instances of bilirubinemia than in the milder cases was cyanosis. With one exception the precise cause of the cyanosis was not found, but a number of these cases were premature infants in whom cyanosis is a common occurrence. However, where we consider the severer cases cyanosis occurred at least as often in the group of full-term infants as among prematures (Table 4).

TABLE 3.—*Relation of Prenatal Factors to Level of Bilirubin*

	Full Term		Premature	
	Total	Bilirubin >20 Mg. /100 Cc.	Total	Bilirubin >20 Mg. /100 Cc.
Mother previously transfused	3	1	4	4
Not previously transfused	21	7	18	12
First pregnancy	7	2	7	4
Multiparous	17	6	15	12
Early rupture of membrane	2	1	7	5
No early rupture of membrane	22	7	15	11

TABLE 4.—*Relation of Clinical Features to Level of Bilirubin*

	Full Term		Premature	
	Total	Bilirubin >20 Mg. /100 Cc.	Total	Bilirubin >20 Mg. /100 Cc.
Jaundice in 24 hr.	8	2	4	2
Jaundice later than 24 hr.	16	6	18	14
Cyanotic	4	4	8	6
Noncyanotic	20	4	14	10
Hemoglobin <15	6	3	2	1
Hemoglobin >15	18	5	19	14

In the group now under discussion there was no evidence of hemolysis, such as anemia or reticulocytosis. There was no correlation between bilirubin and hemoglobin levels (Figs. 3 and 4).

In no case was there evidence of obstructive jaundice or progressive liver disease. Liver-function studies in the 20 infants tested were normal; however, in one case the cephalin flocculation was 2+, but on follow-up became negative. Direct bilirubin levels ranged from 0.05 to 1.3 mg. per 100 cc. Syphilis was excluded by appropriate serologic methods and lack of any clinical signs. Other infections commonly considered as causes of neonatal jaundice and designated by the general term "sepsis" were less easily demonstrated or eliminated from the diagnosis. Because of the difficulties in objective diagnosis, blood cultures were taken routinely. Only three positive blood cultures were found in the full-term group. The infants in question were not ill, and the organisms found in two cases, Staphylococcus albus (coagulase negative) and Escherichia coli, may have been contamin-

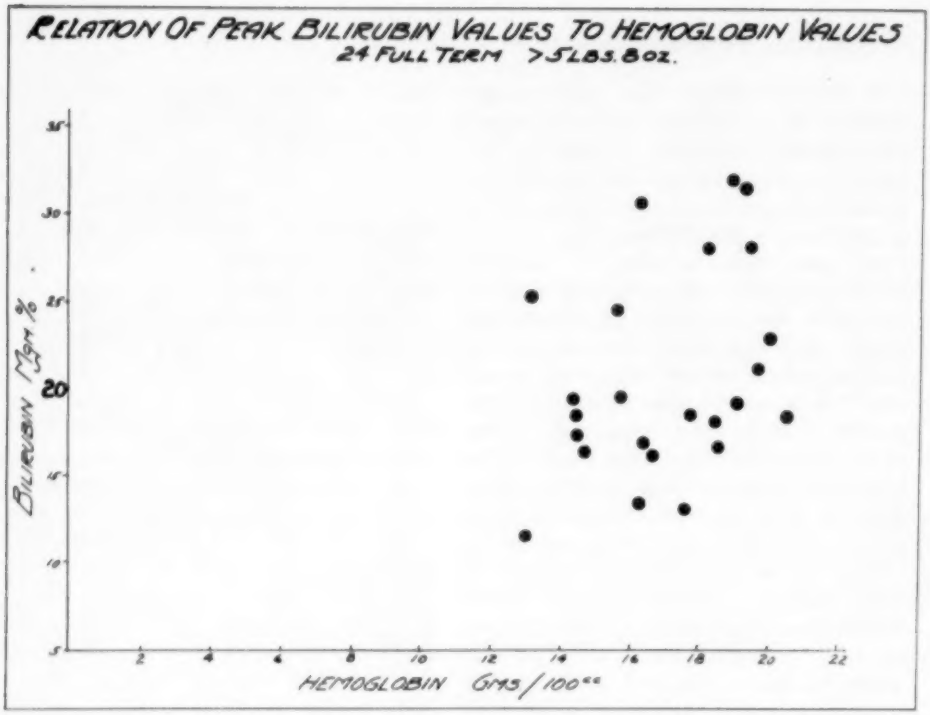

Fig. 3.—Scattergraph showing relation of peak bilirubin values to hemoglobin in full-term infants.

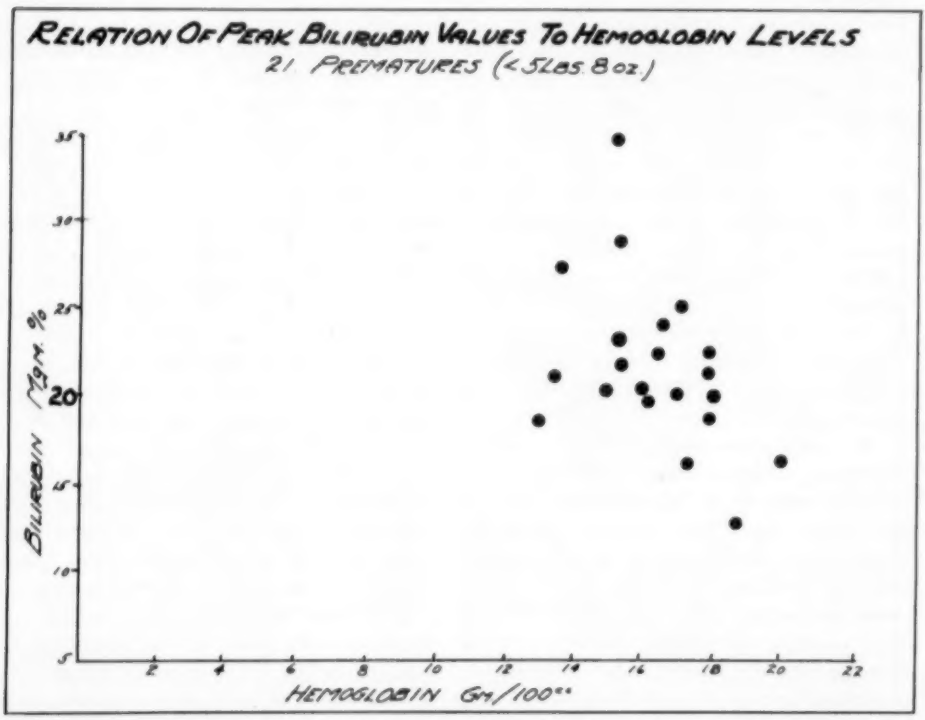

Fig. 4.—Scattergraph showing relation of peak bilirubin values to hemoglobin in premature infants.

TABLE 5.—*Summary of Clinical Findings—Full-Term Infants*

Case No.	Race	Sex	Maternal Parity	Prenatal History	History of Early Rupture of Membranes	Delivery	Birth Weight, Gm.	Clinical Findings					Laboratory Findings					Outcome
								C. C.	Temperature Above 100 F	Resp. Distress	Cyanosis	Lethargy	Onset of Jaundice	Peak of Bilirubin	Hemoglobin Gm./100 Cc.	Blood Culture	Exchange Transfusion	
													Day	Day	Mg./100 Cc.			
1	W	M	3	Mother anemic, transfused	0	Normal	3100	Jaundice	Yes	0	0	0	2	4	19.6	22.4	Neg.	No	Recovered
2	N	M	1		7 days	Normal	2500	Resp'tory distress; jaundice	Yes	++	+	+	3	5	28.6	19.4	Neg.	Yes	Recovered
3	N	M	2		0	Normal	2950	Jaundice	No	0	0	+	2	8	18.0	15.5	Neg.	No	Recovered
4	N	F	1	Labor 33 hr.	0	Low forceps	2700	Jaundice	No	0	0	0	2	2	19.0	17.9	Neg.	No	Recovered
5	W	F	1		0	Manual rotation & low forceps	3430	Early jaundice	No	0	0	+	1†	2	12.7	18.9	Neg.	No	Recovered
6	W	M	3	Mother previously transfused	0	Marginal separation of placenta	2870	Jaundice	Yes	+	0	+	2	4	30.8	12.2	Neg.	Yes	Recovered
7	N	M	1		0	Cord about neck	2870	Jaundice	No	0	0	+	2‡	3	18.2	14.5	Neg.	No	Recovered
8	N	M	2		0	Normal	2890	Jaundice	No	++	+	+	2‡	3	24.5	15.0	Neg.	No	Recovered
9	W	M	6	Diabetes; bleeding during pregnancy	0	"Difficult"; clavicle fractured	4900	Jaundice Cyanosis	X2 Yes	+	+	0	1	3	28	18.1	Neg.	Yes	Recovered
10	N	M	1		0	Normal	3230	Jaundice	No	0	0	±	1†	3	16.6	16.5	Neg.	No	Recovered
11	W	M	9	Mother anemic	0	Normal	3900	Jaundice	No	0	0	0	2	4	16.2	14.9	Neg.	No	Recovered
12	W	F	2		0	Normal	2500	Jaundice	No	0	0	0	3	5	14.4	18.8	Staph. albus coag. Neg. E. coli	No	Recovered
13	N	F	2		0	Normal	3150	Jaundice	Yes	0	0	0	5	5	16.2	18.2		No	Recovered
14	W	F	2		0	Marginal separation	3180	Jaundice	No	0	0	0	2	3	17.9	18.9	Neg.	No	Recovered
15	W	F	5		1 day	Normal	2920	Jaundice	No	0	0	0	1†	4	19.6	19.4	Neg.	No	Recovered
16	N	M	4		0	Normal	4110	Cyanosis Jaundice	No	0	+	0	2‡	5	20.3	16.0	Neg.	No	Recovered
17	W	F	3		0	Normal	4370	Jaundice	Yes	0	0	0	1	3	17.2	14.5	Neg.	Yes	Recovered
18	N	M	2	Mother previously transfused	0	Normal	3690	Jaundice	No	0	0	0	1*	1	11.8	13	Neg.	No	Recovered
19	W	M	1		0	Low forceps	4050	Jaundice	Yes	0	0	0	2	4	32.2	19	Neg.	No	Recovered
20	W	F	3		0	Normal	2500	Jaundice	Yes	0	0	0	1*	1	18.5	18.5	Neg.	Yes	Recovered
21	W	F	2		0	Normal	2890	Jaundice	No	0	0	+	1*	5	23	20	Neg.	No	Recovered
22	N	M	2		0	Normal	2890	Jaundice	No	0	0	0	3	5	25.8	13.6	β-Hem. Strep.	Yes	Recovered
23	W	M	1		0	Normal	3690	Jaundice	No	0	0	+	2	3	13.5	16.1	Neg.	No	Recovered
24	W	M	5		0	Normal	4110	Jaundice	No	0	0	0	?	5	18.6	21.2	Neg.	No	Recovered

*Eighteen hours or less.
†Nineteen to twenty-four hours.
‡Twenty-five to thirty hours.

TABLE 6.—*Summary of Clinical Findings—Premature Infants*

Case No.	Race	Sex	Maternal Parity	Prenatal History	History of Early Rupture of Membranes	Delivery	Birth Weight, Gm.	Clinical Findings				Laboratory Findings						
								C. C.	Temperature Above 100 F	Resp. Distress	Cyanosis	Lethargy	Onset of Jaundice	Peak of Bilirubin	Hemoglobin Gm/100 Cc.	Blood Culture	Exchange Transfusion	Outcome
													Day	Day	Mg/100 Cc.				
1	W	M	1		5 days	Low forceps	1790	Prem.	Yes	0	0	0	1†	4	21.2	17.9	Neg.	Yes	Recovered
2	W	F	2	Mother previously transfused	1 mo.	Normal	980	Prem.	Yes	+	+	0	2	4	21.2	17.9	Hem. Staph. aureus coag.+	Yes	Recovered
3	W	F	1		0	Unattended	1590	Prem. & jaundice	No	0	0	0	5	6	25	17.7	Hem. Staph. aureus coag.+	Yes	Recovered
4	W	M	3	Bleeding during last trimester	0	Normal; respiration delayed	1840	Prem.	No	0	+	0	3	4	21.2	16.3	Neg.	Yes	Recovered
5	W	M	3		4 days	Normal	1474	Prem.	No	+	+	0	4	5	18.6	17.9	Neg.	No	Recovered
6	W	M	1		0	Normal	1620	Prem.	No	±	+	0	3	6	15.7	17.0	Neg.	No	Recovered
7	W	F	4		2 days	Normal	1080	Prem.	No	±	0	0	3	5	20.6	13.6	Neg.	Yes	Recovered
8	W	F	4		0	Unattended	1590	Prem.	No	+	+	0	4	4	28.8	15.3	Neg.	Yes	Recovered
9	W	F	1		0	Unattended—child Badly Bruised	1130	Prem.	No	±	0	0	1†	4	18.5	12.3	Neg.	No	Died; kernicterus
10	W	M	5		0	Normal	1130	Prem.	Yes	±	0	0	2	3	16.6	20	Neg.	No	Recovered
11	W	F	9		0	Normal	2440	Jaundice	No	0	0	++	2	3	22	17.9	Neg.	Yes	Retarded
12	W	M	5	Mother anemic; transfused	0	Face presentation	2240	Jaundice	No	0	0	+	2	5	27	17.5	Neg.	No	Recovered
13	W	M	7		2 days	Normal	1870	Prem.	Yes	0	0	0	3	4	21.4	16.1	Neg.	Yes	Recovered
14	W	M	4	Mother previously transfused	0	Normal	2010	Prem.	No	+	+	0	1†	6	23.6	18.4	Hem. Staph. aureus coag.+	Yes	Recovered
15	W	M	4		0	Precipitate	2270	Jaundice	Yes	0	+	+	6	6	32	15.3	Neg.	No	Died; kernicterus
16	W	M	3		0	Normal	2240	Jaundice	No	0	0	+	1*	2	13	18.8	Neg.	No	Recovered
17	W	M	1		2 days	Normal	2210	Prem.	No	+	+	0	4	4	20	17.9	Hem. Staph. aureus coag.+	Yes	Recovered
18	W	F	1	Bleeding during pregnancy	1 mo.	Low forceps	1670	Prem.	Yes ×2	+	+	+	2	5	19.6	15.4	Neg.	Yes	Died
19	W	F	3		0	Normal; resp. delayed	2210	Jaundice & prem.	No	0	0	0	3	6	26.2	—	β-hem. Strep.	Yes	Recovered
20	N	M	2	Threatened abortion	0	Normal	1620	Prem.	No	0	0	0	3	4	20.3	16.2	Neg.	Yes	Recovered
21	N	M	1		0	Low forceps	1620	Prem.	Yes ×3	0	0	+	4	5	23.6	15.3	E. coli	Yes	Recovered
22	N	F	3	Mother previously transfused	0	Normal	1640	Jaundice & prem.	No	±	0	0	3	3	20.6	18.4	E. coli	Yes	Recovered

*Eighteen hours or less.
†Nineteen to twenty-four hours.
‡Twenty-five to thirty hours.

TABLE 7.—*Relation of Therapeutic Agents to Level of Bilirubin*

Therapy	Full Term		Premature	
	Total	>20 Mg. /100 Cc.	Total	>20 Mg. /100 Cc.
O_2	5	4	11	7
No O_2	19	4	11	9
Vitamin K	15	5	22	16
No vitamin K	9	3	0	0
Sodium sulfadiazine	20	6	11	10
No sodium sulfadiazine	4	2	11	6

TABLE 8.—*Number of Infants in Each Group Who Had Exchange Transfusions*

Bilirubin, Mg/100 Cc.	No. Cases	Exchanged	Not Exchanged	K*
Full Term				
Levels >20	8	5	3	
Levels <20	16	1	15	
Total	24	6	18	
Premature				
Levels >20	16	14	2	1
Levels <20	6	1	5	1
Total	22	15	7	2

*Kernicterus

ants. The culture in the third case yielded beta-hemolytic Streptococcus. The blood cultures of four premature infants were positive for hemolytic Staphylococcus aureus (coagulase positive) an organism generally considered of pathogenic significance. The bilirubin levels of these patients exceeded 20 mg. per 100 cc., but a similar elevation was found in 9 of 16 premature infants whose blood cultures were sterile. Two other cultures were positive for E. coli and one for beta-hemolytic Streptococcus. The one premature infant in whom the culture was positive for E. coli was the only one who had clinical evidence of infection. The temperature rose to 101 F for three days during the first week and petechiae were noted on the fifth day. No other child showed such signs. Tables 5 and 6 show the outline of clinical symptoms and pertinent facts in relation to history in both the full-term and premature group.

Table 7 shows the relation of bilirubin level to treatment with oxygen, vitamin K, and sodium sulfadiazine. No influence on the degree of bilirubinemia is seen. No infant received sulfisoxazole (Gantrisin).

As for the general outlook for the group, there were no fatalities or demonstrable neurologic residues in the full-term infants during the limited period of this study. In the premature group three infants died, one on the sixth, one on the seventh, and one on the ninth day of life. At autopsy kernicterus was found in two of these infants. The maximum bilirubin levels in the babies with kernicterus were 18.5 mg. per 100 cc. and 32 mg. per 100 cc. These two infants had not had exchange transfusions, and neither had received sulfadiazine (Table 8). No kernicterus was found in the third premature infant who died on the ninth day of life. This infant had been exchanged on the fifth day, at which time the bilirubin level was 19.6 mg. per 100 cc. There had been respiratory distress from the second day. One other premature infant whose birth weight was 2440 gm. (5 lb. 6 oz.) who was lethargic during the first week of life, and who had a serum bilirubin level greater than 20 mg. per 100 cc. for over 4 days does not sit at age 9 months and had a persistent Moro reflex till age 8 months. This infant is believed to have suffered neurologic damage. One exchange was done on the third day of life but subsequent exchange transfusions were not done and the bilirubin level remained over 20 mg. per 100 cc. for three more days. Two other infants whose bilirubin levels were over 20 mg. per 100 cc. for 5 and 6 days are doing well at 5 and 8 months, respectively. Clearly one cannot correlate the occurrence of kernicterus with a critical level of bilirubin.

Comment

Evidence has been accumulating,[6-8] and the data presented here again show that in prematures, for reasons not yet known, there is a tendency toward excessive bilirubinemia. By taking blood groups into account and thus eliminating the element of hemolysis, it has been possible to demonstrate that the same phenomenon occurs with appreciable though probably less frequency in the apparently healthy full-term baby and that the same range of levels may be attained as are commonly encountered in hemolytic disease. The patterns observed are in accord with

the view that the significant factors and changes in bilirubin metabolism in our patients reside in changes in liver function. It seems reasonable to assume that this function is related to the conversion of so-called indirect bilirubin to direct bilirubin. Recently Billing and Lathe [9] have indicated that the excretion of indirect bilirubin involves its conversion to a direct-reacting water-soluble pigment and that the main pathway is probably through conjugation with glucuronic acid. This conjugation is further confirmed by the recent work of Dr. Rudi Schmid,[10] who has found that hydrolysis of the azo-pigment of direct bilirubin yields the azo-pigment of indirect bilirubin and glucuronic acid.

What role the liver plays in this possible conjugation is not known,* nor do we have any data concerning the relation of carbohydrate metabolism and available glucuronic acid to the development of this function in the newborn. Definition of the possible enzyme system involved and influence of prenatal and paranatal factors, including placental function, on the development of the ability to metabolize bilirubin seems indicated if we are to understand the mechanism of hyperbilirubinemia. Simply because the mechanism cannot now be distinguished from that responsible for the lower degrees of bilirubinemia commonly seen in the newborn, we are not entitled to speak of physiologic icterus in a group whose bilirubin values deviate so markedly from the average. A redefinition of physiologic jaundice is needed all the more because our experience and that of others [6,7] shows that, in prematures at least, this nondescript hyperbilirubinemia can be associated with neurologic sequelae. Further, the association of kernicterus, prematurity, and jaundice has been noted by a number of authors.[11-14]

* Since this manuscript was submitted, conjugation of bilirubin with glucuronic acid in vitro has been achieved by Rudi Schmid using a system containing guinea-pig-liver microsomes and uridine diphosphoglucuronic acid (UDPGA); personal communication to the authors.

The question of a therapeutic approach to hyperbilirubinemia has practical as well as theoretical implications. We are not prejudging the question as to whether elevated levels of bilirubin in the absence of hemolytic disease represent a valid indication for therapy. In the present group 15 premature infants and 6 full-term infants were exchanged but no systematic attempt has been made as this group came under study to set up criteria for exchange. Generally, the philosophy of management was based on the presence of relatively high values early and expectation of further rise in bilirubin or on the presence of excessively high values. No fixed critical values were regarded as indications for exchange, although in practice the level of 20 mg. per 100 cc. was taken as a rough guide in analogy to the recommendations made for second and third exchange transfusions in hemolytic disease by Diamond et al.[15,16]

Whether the use of this level as an indication for exchange is justifiable under these circumstances, particularly in the premature, is not known. The finding of kernicterus in premature infants who have never had bilirubin levels of this degree has been reported.[7,8] An appraisal of the efficacy of exchange under these circumstances will be presented in the following paper.

Summary

A descriptive analysis has been given of a group of infants in whom bilirubinemia was present in excess of levels usually regarded as physiologic in absence of hemolytic disease or significant incompatibility between mother and child. In three cases evidence of congenital hemolytic anemia was found. In one instance a cyst of the liver with hepatitis was diagnosed. In the remaining group no cause or mechanism was found. The only factors encountered with sufficient frequency to suggest correlation were birth weight and cyanosis, but in the majority of cases nothing unusual was observed.

The process associated with excessive bilirubinemia appeared to be an extension of what is commonly called physiologic jaundice. However, in view of the demonstrated hazard to the central nervous system, particularly in prematures, a more exact definition of physiologic jaundice is required. Consideration must be given to the question of whether, or when, exchange transfusion should be done in hyperbilirubinemia in the absence of hemolytic disease.

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Studies in Hyperbilirubinemia

II. Clearance of Bilirubin from Plasma and Extravascular Space in Newborn Infants During Exchange Transfusion

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With the Technical Assistance of Loula Woodcock

The preceding paper dealt with the occurrence of hyperbilirubinemia with levels comparable to those encountered in hemolytic disease of the newborn, in full-term and premature infants exhibiting no evidence of either hemolytic or hepatic disease. The serum bilirubin in some of the patients in this group of 46 infants was of a magnitude which in hemolytic disease would be associated with a high incidence of kernicterus and is therefore generally regarded as an indication for exchange transfusion. The rationale of an exchange transfusion in the treatment of hemolytic disease may not be generally agreed upon, but it would seem that most investigators perform the procedure with the chief aim of removing vulnerable sensitized red cells, thereby decreasing the potential for bilirubin formation resulting from the accelerated breakdown of hemoglobin. Secondarily an exchange transfusion can be expected to remove a certain amount of bilirubin directly by the exchange of plasma involved in the procedure. The efficacy of this latter function of an exchange has not been fully evaluated.

In hyperbilirubinemia unaccompanied by accelerated hemolysis, the direct removal of bilirubin would seem to be the sole purpose of an exchange transfusion, since nothing would be gained by replacing normally surviving red corpuscles with donor blood. By the same token, the direct removal of bilirubin would appear to be the major if not the sole purpose of a second, third, or fourth exchange transfusion, as often advocated in hemolytic disease, when the serum bilirubin fails to remain at satisfactory levels after the first exchange transfusion. In such cases the large majority of the infant's original sensitized red blood cell population has already been removed by the first exchange.

The situation thus common to infants with nonhemolytic hyperbilirubinemia and to once-exchanged infants with hemolytic disease permits an appraisal of the efficacy of exchange transfusion as a means of removal of bilirubin. Such an appraisal is the purpose of the present paper. In presenting our observations we do not by any means imply that the indications arising from hyperbilirubinemia in hemolytic disease can be directly applied to hyperbilirubinemia from other causes.

For reasons which will shortly become obvious the efficacy of an exchange transfusion cannot be gauged by the serum bilirubin concentration determined immediately after the procedure. It is common experience that following an exchange transfusion in the icteric newborn infant there is a "rebound" phenomenon. The predictability of this phenomenon is at present a major problem from both the practical and the theoretical viewpoint. Allowing for variations in age, in amounts used and time elapsed during the procedure, in the development of hepatic function, and in the

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presence or absence of a continued hemolytic process, the height and duration of the rebound phenomenon is highly variable. This is particularly true in premature infants, but it is also true in patients given exchange transfusion for hemolytic disease and to a less extent in full-term infants with hyperbilirubinemia of undetermined cause.

Figures 1 to 3 illustrate the variety of patterns observed by us.

In the cases of hyperbilirubinemia without hemolytic disease (Fig. 1 and 2) the bilirubin levels of infants who had received exchange transfusion are compared not with those of a normal group but with the average bilirubin levels obtained within the group of hyperbilirubinemic infants who were not subjected to this procedure. This seemed to be a fairer test of the efficacy of exchange transfusions than would be a comparison with normal infants. Evaluated on this basis it will be seen that in two of the premature infants (Fig. 2, Cases E and H) the bilirubin values following exchange transfusion returned to levels slightly above average for the group as a whole despite an initial very satisfactory drop and that the curves thereafter paralleled the untreated controls. By contrast, the two other examples shown (Fig. 2, Cases F and G) with comparable preexchange levels responded far more favorably, showing only a minor rebound followed by further rapid decline of the bilirubin level. Such a comparison does not imply that in the less favorable cases the exchange transfusion was totally without effect. It seems at least likely that in the two cases in question (Fig. 2, Cases E and H) further rise of the bilirubin was prevented by the procedure. However, the fact remains that in these and similar instances despite the exchange transfusion the serum bilirubin concentration returns to and persists at a level which may be dangerous, whereas in other instances a far greater effect seems to be achieved. The point we wish to make is that such variations in the response to exchange transfusion suggest the influence of factors other than the exchange itself.

The likeliest such factor would seem to be the existence of a variable extravascular reservoir of bilirubin which may diffuse in or out of the plasma. In support of this

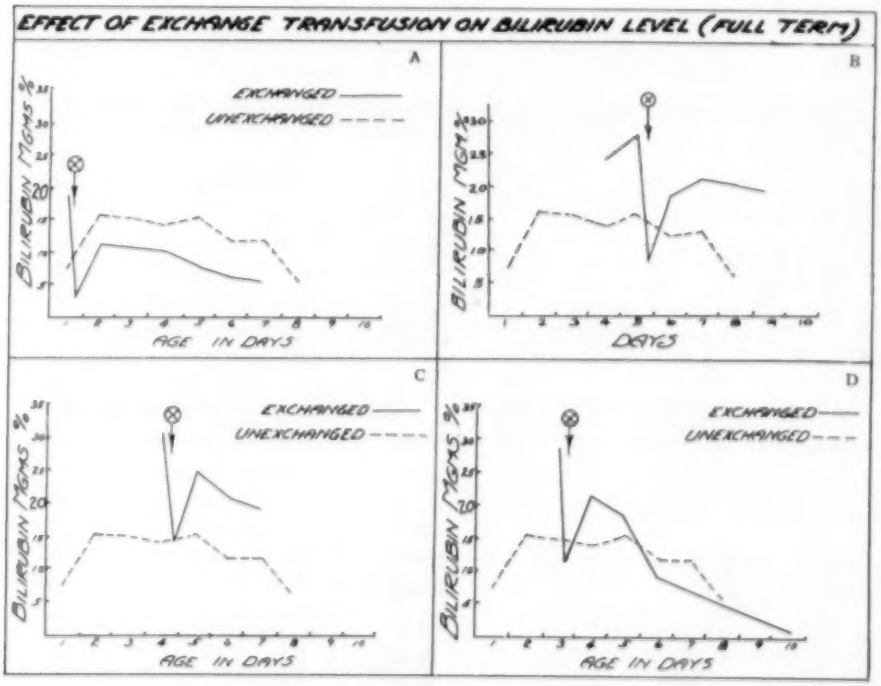

Fig. 1.—Effect of exchange transfusion on bilirubin levels in full-term infants with hyperbilirubinemia. Solid line represents levels in individual cases who received exchange transfusions. The dotted line represents the average daily serum bilirubin levels for a group of full-term infants with hyperbilirubinemia who were not exchanged.

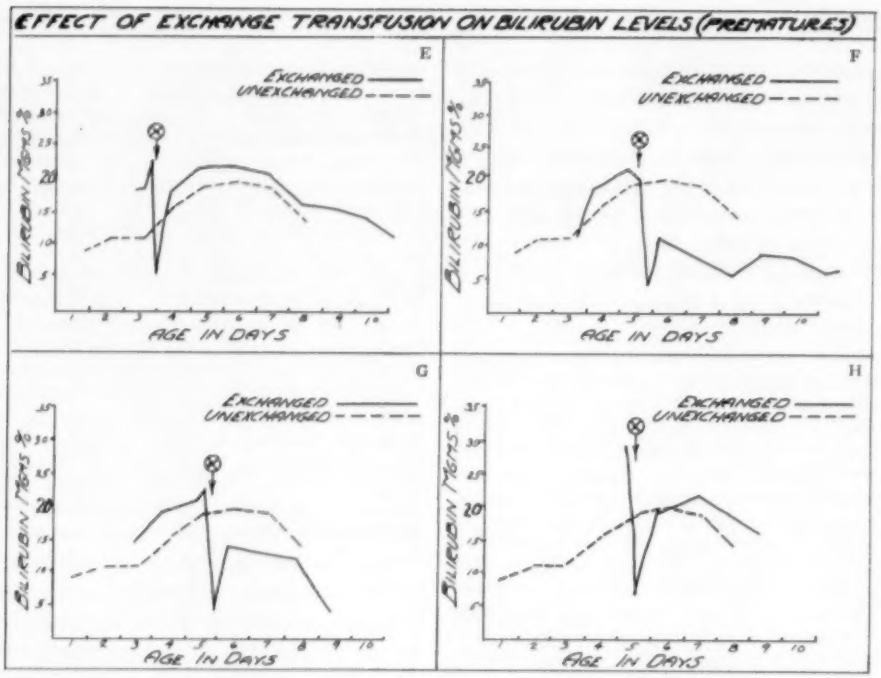

Fig. 2.—Effect of exchange transfusion in bilirubin levels in premature infants with hyperbilirubinemia. Solid line represents levels in individual cases who received exchange transfusion. The dotted line represents the average daily serum bilirubin levels for a group of premature infants with hyperbilirubinemia who were not exchanged.

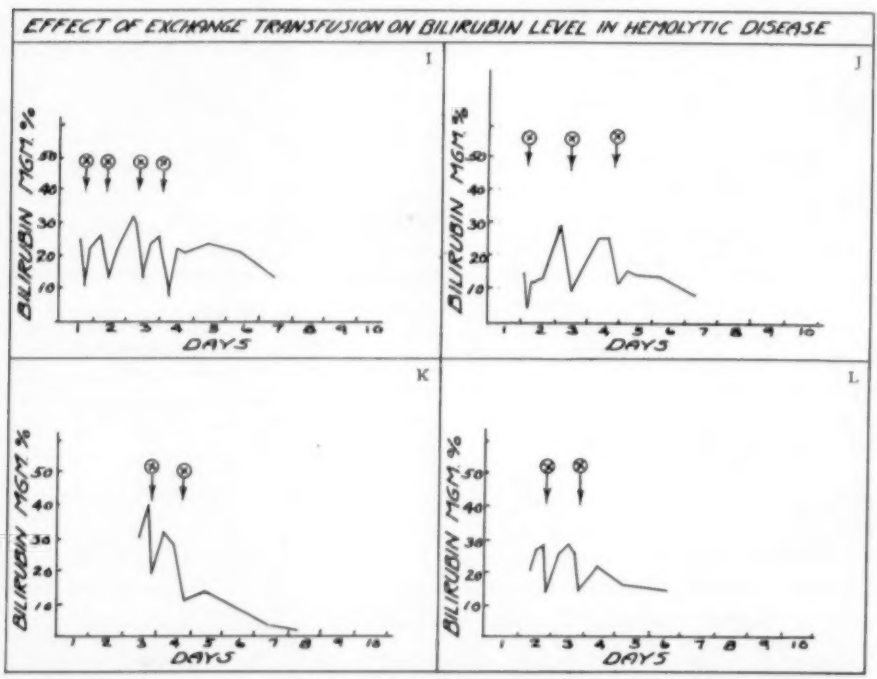

Fig. 3.—Rebound of serum bilirubin level in infants with Rh and ABO hemolytic disease requiring more than one exchange transfusion. Circled "X" with downward arrow indicates exchange transfusion.

concept it has been our observation that the rate of increase of the plasma bilirubin concentration in the rebound phase is as a rule more rapid than was the initial rate of accumulation of plasma bilirubin prior to exchange transfusion. This apparent acceleration following the exchange has been particularly evident in infants not exhibiting evidence of hemolysis whose initial bilirubin accumulation was more gradual.

The work of Lathe [1] and of Stempfel [2] further tends to indicate that bilirubin enters the plasma during exchange. These authors have observed discrepancies between the red blood cell mass removed as measured by differential cell agglutination technique and the amount of bilirubin removed during exchange transfusion. More bilirubin remained in the plasma at the end of an exchange transfusion than was expected on the basis of the cell exchange accomplished. However, this work was done on patients with hemolytic disease, where the possible influence of continued hemolysis during and especially following the exchange transfusion must be considered. The possible breakdown of residual and newly formed erythrocytes might account at least in part for the reaccumulation of the pigment, and for this reason an accurate evaluation of the factor represented by the movement of bilirubin from extravascular to intravascular space is difficult. In patients with hyperbilirubinemia not related to demonstrable hemolysis and in those with hemolytic disease who have already undergone one or two exchange transfusions, the factor of accelerated *de novo* formation of bilirubin is negligible.

In the experiments to be presented the extent of the exchange of red blood cells was taken as an index of the total blood volume exchange. If the percentage of the original red cell mass remaining at any given point is a valid index of the completeness of the exchange, any divergencies in the concentration of bilirubin must of necessity represent diffusion effect in one or the other direction. Instead of the more tedious Ashby procedure, the determination of the concentration of fetal hemoglobin was chosen as a means of tagging the infants' red blood cells.

Experimental Procedure

A. *Collection of Samples*

Exchange transfusions were performed on seven infants through the umbilical vein using the intermittent method. Samples of 10 cc. were removed and replaced. Of each 10 cc. received a 3 cc. aliquot was collected in an individual tube, and microhematocrit, bilirubin, and fetal hemoglobin determinations were made on these samples. Each remaining 7 cc. was pooled in a large collecting bottle containing heparin. At the end of the procedure this volume was measured and microhematocrit, bilirubin, and fetal hemoglobin determinations were also made on an aliquot taken from this bottle.

B. *Method*

1. Bilirubin was determined by a modification of the method described by Powell.[3] The modification consisted of shortening to five minutes the time allowed after addition of sodium benzoate urea before reading the per cent transmission. This reading gives the total bilirubin.

2. Fetal hemoglobin was determined by the method of Singer.[4]

3. Estimates of blood volume were made from the determinations of fetal hemoglobin making the following assumptions:

(a) the blood volume remains constant throughout the exchange transfusion,

(b) the fetal hemoglobin concentration in the individual venous samples are representative of the fetal hemoglobin concentration in the infant at the time of collection, and

(c) the concentration of fetal hemoglobin in the total blood removed when adequate care and sampling is taken is representative of total fetal hemoglobin removed. On the basis of these assumptions the following calculation can be made: Pretransfusion grams of fetal hemoglobin equals total grams of fetal hemoglobin removed plus grams of fetal hemoglobin remaining in the circulation.

(pretransfusion gm. Hb/100 cc.×% fetal Hb×BV*) =
(total gm. Hb/100 cc.×% fetal Hb×BV removed) +
(post-transfusion gm. Hb/100 cc.×% fetal Hb×BV).

Solved for blood volume:

* Blood volume expressed in cubic centimeters×100.

$$\frac{\text{Total gm. Hb/100 cc.} \times \% \text{ fetal Hb.} \times \text{vol. removed}}{\text{Pre gm. Hb/100 cc.} \times \% \text{ fetal Hb.} - \text{post gm. Hb/100 cc.} \times \% \text{ fetal Hb.}}$$

Calculations made in this manner have given values for blood volume ranging from 96-129 cc. per kilogram body weight. These findings are in substantial agreement with those of Mollison et al.,[5] who used tagged erythrocytes as well as the dye technique, and with the results of Schulman and Smith[6] and others[7] using the dye technique. However, for the purposes of this discussion it is immaterial whether the measured blood volumes are used or a figure of 100 cc. per kilogram is taken to be a representative figure in estimating blood volume.

The fetal hemoglobin was determined in the initial sample. Together with the initial blood volume and hemoglobin concentration this value permitted calculation of total fetal hemoglobin in grams. This may be taken as representative of total red blood cell mass. On each subsequent sample a similar determination was made so that the actual amount of fetal hemoglobin in grams in each sample was known. From these values it was possible to construct a curve representing the amount of fetal hemoglobin remaining in the body at any given point during the exchange by using the formula:

$$\frac{\text{gm. fetal Hb. in sample}}{\text{gm. initial fetal Hb.}} \times 100 = \% \text{ fetal Hb. remaining in circulation.}$$

These points are plotted in Figures 4-8.

Similar curves were constructed at identical intervals for the amount of bilirubin remaining in the plasma. The following calculations serve to determine these values. Taking hematocrit into account the plasma volume was calculated. The initial bilirubin concentration then permitted calculation of the total bilirubin content. By determining the amount of bilirubin in each sample the per cent of the initial bilirubin remaining could be determined by the following formula:

$$\frac{\text{Total bilirubin (mg.) in plasma sample}}{\text{Total initial bilirubin (mg.) in plasma}} \times 100 = \% \text{ bilirubin remaining in circulation.}$$

Observations

The data pertaining to the procedure of exchange transfusion in the seven cases studied in the manner described are presented in the Table. It will be seen that there were differences in the total amount of blood exchanged in a given patient. Although the amounts exchanged were based roughly on the weight and approximate calculated blood volume in each case, it will be seen that the volume exchanged per unit of body weight also varied considerably from case to case. Nevertheless, the comparisons between the efficiency of removal of red cells versus that of bilirubin are valid because they are based on the actual determination of the residual red blood cell mass (as fetal hemoglobin) and of total residual bilirubin, irrespective of the absolute and relative amounts of blood exchanged.

Figure 4, Case 1, demonstrates a very large discrepancy at the end of the exchange transfusion between the residual red cell mass, expressed as per cent of original mass of fetal hemoglobin, and the "residual" bilirubin in the plasma. The calculations in this instance were based on the blood volume as actually determined rather than estimated. In this instance the absolute amount of bilirubin present in the plasma at the beginning of the procedure was 22 mg. The amount actually removed was likewise 22 mg. It follows from the fact that at the end of the procedure 13 mg. was present in the infant's circulating plasma that this amount represents bilirubin which has newly entered the vascular space during the exchange. The seeming discrepancy between the residual red blood cell mass and the "residual" bilirubin thus finds its explanation.

These findings indicate, as does the shape of the curve, that after relatively rapid initial removal of bilirubin, a gradient from the extravascular space into the plasma is established which in this instance replenishes the plasma bilirubin while the red blood cell mass continues to be removed at a rapid rate. One would therefore expect the persistence of substantial amounts of bilirubin in the tissues at the end of an exchange

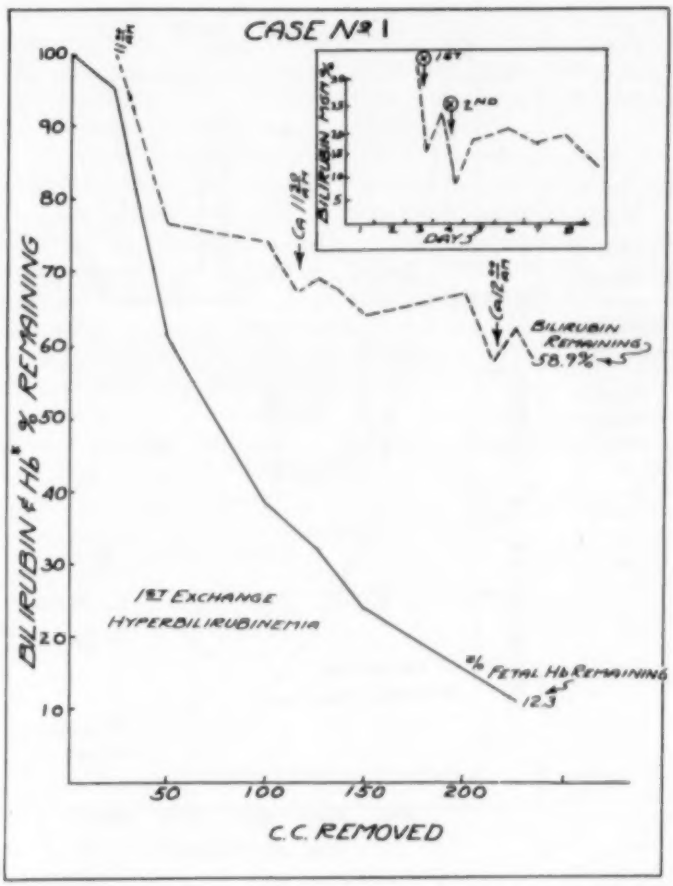

Fig. 4.—Comparison of the removal of bilirubin and of cells (represented by fetal hemoglobin) during exchange transfusion (see text). Time is indicated at beginning and end of exchange as well as at points when calcium was given. Insert indicates the daily serum bilirubin levels.

* Hemoglobin in ordinate refers to per cent of initial fetal hemoglobin remaining at any point on the curve.

transfusion in such a case. Therefore, assuming that effective excretion by the liver remains in abeyance, an appreciable secondary rise of the plasma bilirubin level should follow establishment of a new equilibrium between tissues and plasma. This expectation is borne out by the curve representing the subsequent concentrations of plasma bilirubin in this patient (Fig. 4 insert, Case 1).

The rapidity with which bilirubin diffuses across the vascular membrane is obviously very great if so marked a divergence between the per cent of removal of bilirubin and that of red blood cells can occur during a procedure accomplished in an hour's time. That this is indeed a very rapid process is shown by the immediate increase in the measured bilirubin level which occurs regularly when the procedure is even momentarily interrupted, as for example during administration of calcium which is accomplished in five minutes. This phenomenon, the immediate rise of the bilirubin level when the rate of exchange is retarded, was repro-

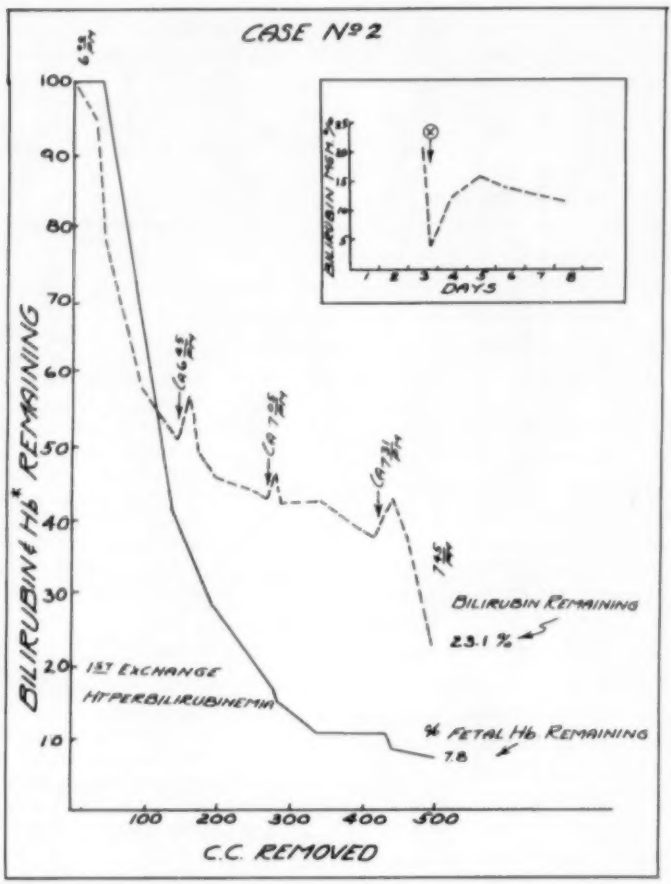

Fig. 5.—Comparison of the removal of bilirubin and of cells (represented by fetal hemoglobin) during exchange transfusion (see text). Time is indicated at beginning and end of exchange as well as at points when calcium was given. Insert indicates the daily serum bilirubin levels.

* Hemoglobin in ordinate refers to per cent of initial fetal hemoglobin remaining at any point on the curve.

ducible (Fig. 5, Case 2) and in itself indicates the existence and influence of a gradient of bilirubin across a highly permeable membrane.

Figure 5, Case 2, illustrates a somewhat different pattern. This patient, likewise a premature infant with hyperbilirubinemia, was left at the end of the exchange transfusion with 7.8% of his original red cell mass and 23.1% of the amount of bilirubin initially present in the plasma. The discrepancy between the two values is considerably smaller than in the previous case. Expressed in another way, the degree to which the bilirubin in the plasma was replenished from the extravascular compartment was substantially less than in the first instance and the subsequent rebound was moderate and not sustained (Fig. 5, insert).

Figure 6, Case 3, illustrates the case of an infant in whom the curves for bilirubin and red blood cell mass were virtually parallel throughout the exchange. The almost equal efficiency of the removal of red blood cells and of bilirubin indicates the absence of a sizeable extravascular reservoir of bilirubin. This expectation was borne out by the subsequent course of the infant showing only a slight and unsustained rebound. It is worth noting that in this case the measurements were made during the second exchange transfusion, which was begun at a time when the bilirubin level

was almost as high as it had been immediately prior to the first exchange transfusion and was still rising. The curve again shows strikingly the effects of a temporary interruption of an exchange transfusion.

Figure 7, Case 4, again demonstrates a fairly appreciable discrepancy between the per cent of bilirubin remaining in the circulation and that of fetal hemoglobin. In this instance the height and the rapidity of the rebound (Fig. 7, insert) was again substantial as expected, but the phenomenon was unsustained in contrast to Figure 4, Case 1, which showed a fairly similar pattern during the exchange transfusion. The rather rapid decline of the plasma bilirubin concentration in Case 4 may be attributed to the improvement of the excretory function of the liver taking place at this point. (The post-calcium effects are not obvious here, since not enough points were plotted in this curve.)

The Table shows that in the seven cases studied the amount of bilirubin removed was either nearly as great as or in some instances greater than the total amount initially present in the plasma. Even in those instances where the amount removed was not quite as large as the total initial amount of bilirubin, more pigment remained in the plasma than could be accounted for by the difference. It follows clearly that in all cases bilirubin had to enter the plasma during the exchange.

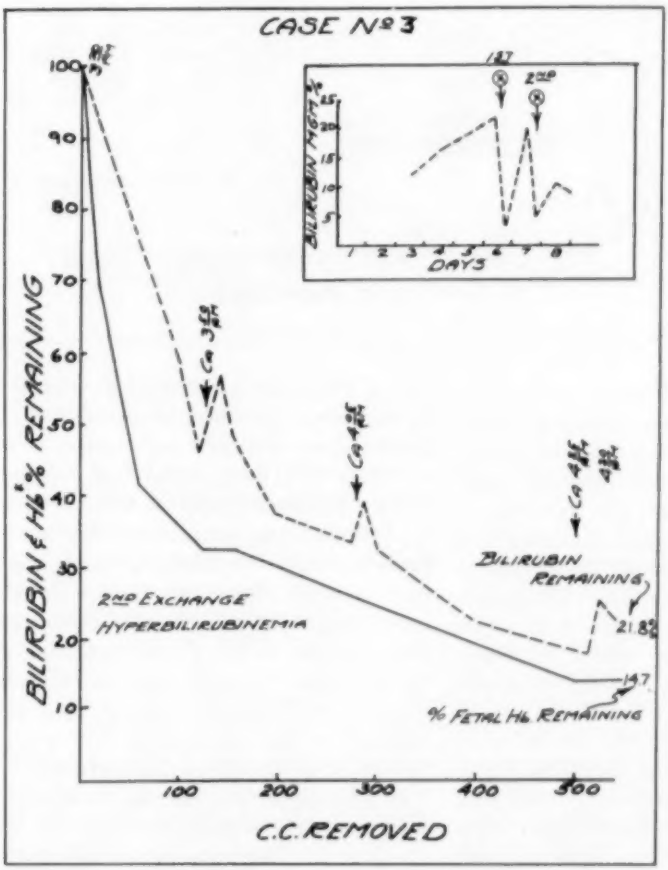

Fig. 6.—Comparison of the removal of bilirubin and of cells (represented by fetal hemoglobin) during exchange transfusion (see text). Time is indicated at beginning and end of exchange as well as at points when calcium was given. Insert indicates the daily serum bilirubin levels.

* Hemoglobin in ordinate refers to per cent of initial fetal hemoglobin remaining at any point on the curve.

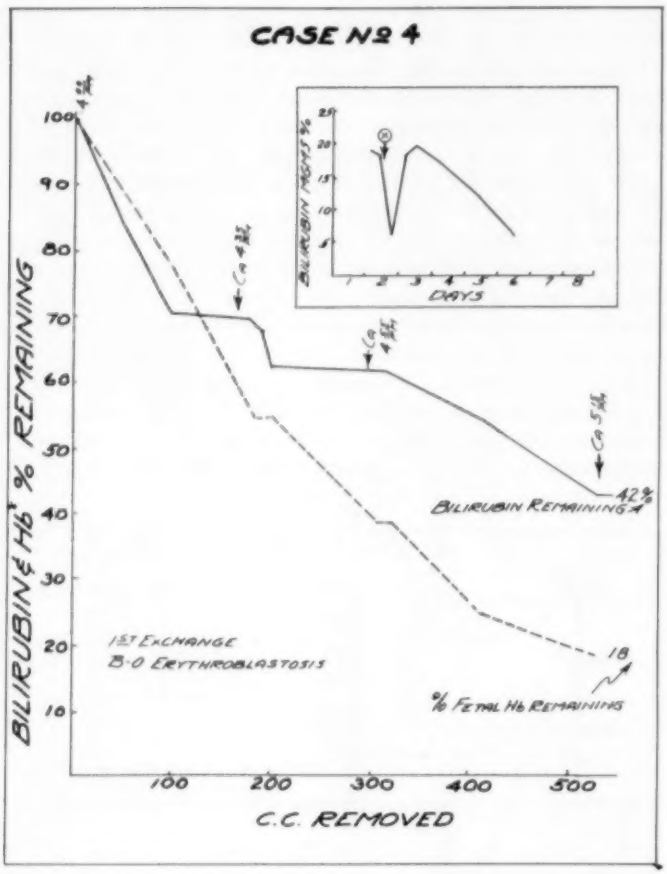

Fig. 7.—Comparison of the removal of bilirubin and of cells (represented by fetal hemoglobin) during exchange transfusion (see text). Time is indicated at beginning and end of exchange as well as at points when calcium was given. Insert indicates the daily serum bilirubin levels.

* Hemoglobin in ordinate refers to per cent of initial fetal hemoglobin remaining at any point on the curve.

Comment

The data presented clearly show that bilirubin accumulates in the plasma during exchange transfusion even while it is being removed. This was particularly striking in those cases in which is could be shown that more bilirubin was taken out of the plasma than had been present initially. The source of the added bilirubin is not likely to be pigment formed as the result of intravascular hemolysis, particularly in Cases 1, 2, 3, and 7, where a hemolytic process was never present. It follows that bilirubin must enter the circulation from the extravascular space at a very rapid rate. This conclusion implies the establishment of a gradient from the tissues to the plasma. This gradient can be appraised by inspection of the curves presented. It is indicated by the point at which the initial steep slope indicating the rapid removal of bilirubin changes to a more nearly horizontal line and the bilirubin and fetal hemoglobin curves begin to diverge. Knowledge of this gradient gives a better idea of the total body bilirubin than does the plasma concentration above because it gives some indication of the amount of bilirubin which has accumulated in the tissues. However, even this information does not provide very precise knowledge of the tissue concentration.

It seems that the bilirubin level represents an equilibrium between plasma and extravascular deposits. It would appear

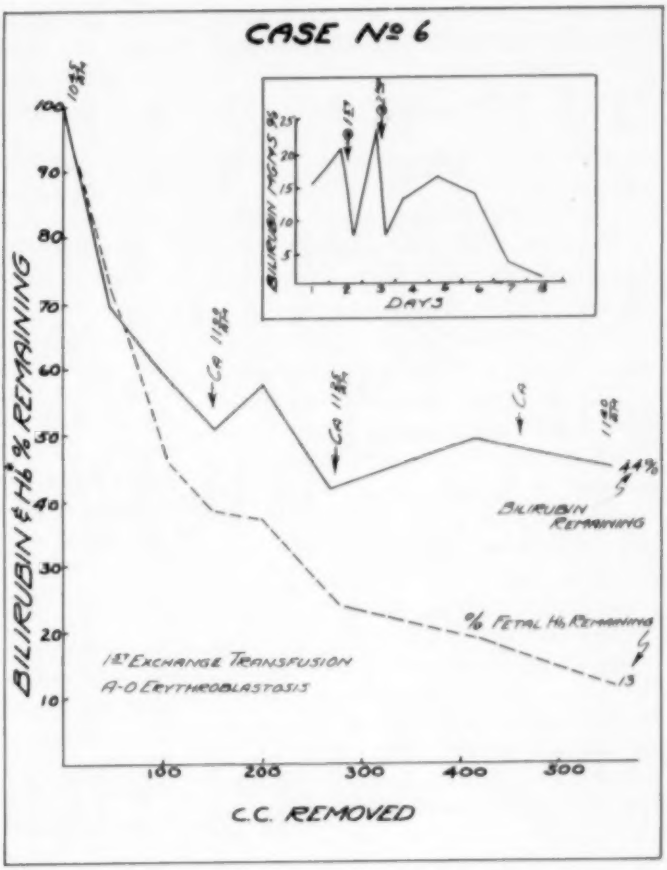

Fig. 8.—Comparison of the removal of bilirubin and of cells (represented by fetal hemoglobin) during exchange transfusion (see text). Time is indicated at beginning and end of exchange as well as at points when calcium was given. Insert indicates the daily serum bilirubin levels.

* Hemoglobin in ordinate refers to per cent of initial fetal hemoglobin remaining at any point on the curve.

from the rapidity of the movement of bilirubin into the plasma during exchange that an immediate equilibration takes place between plasma and extracellular fluid. It is evident that in the icteric patient the tissues themselves contain bilirubin within the cells. There must therefore be another gradient and another equilibrium occurring between intracellular and extracellular concentrations of bilirubin. The factors which determine the direction and rate of this movement are not yet apparent. No doubt it must be influenced by the plasma—extracellular fluid equilibrium itself and, in addition, such factors as differential affinity of different tissues or cells for bilirubin might play a part.

There is evidence that bilirubin in the plasma is associated with protein.[8] The degree to which these proteins are saturated with bilirubin is likely to influence the shift of bilirubin from tissue to plasma and vice versa, for, as Lathe[9] has pointed out, at great concentrations of bilirubin the affinity of protein for the pigment may be less and tissue-binding sites, such as skin, intima of blood vessels, conjunctivae, and intestinal mucosa,[10] may compete for bilirubin. The reverse might take place during exchange as unsaturated protein is added to the plasma and as bilirubin is removed.

Influence of permeability factors are suggested by the observation of Stempfel[11] showing that the concentration of bilirubin

Data Pertaining to Procedure of Exchange Transfusion

Case No.	Diagnosis	Birth Weight		Age*	Hematocrit	Amount Exchanged	Blood Volume	Ratio: Exchange Vol. / Blood Vol.	Bilirubin: Serum Concentration per 100 Cc. Pre Exchange	Bilirubin: Serum Concentration per 100 Cc. Post Exchange	Bilirubin: Apparent Efficiency of Removal	Bilirubin: Total Plasma Content Pre Exchange	Bilirubin: Total Plasma Content Post Exchange	Bilirubin: Amount Removed	Bilirubin: Amount Presumed to Have Entered Plasma	True Efficiency of Removal	Efficiency of Cell Removal
		Lb.	Oz.			Cc.	Cc.				%	Mg.		Mg.	Mg.	%	%
1	Premature; hyperbilirubinemia	2	8	3 days	50	230	measured† 130 estimated‡ 114	2.0	33.6	15.8	41.1	measured 22.0 estimated 19.3	13.0 11.4	22.0 19.3	13.0 11.4	100	87.7
2	Premature; hyperbilirubinemia	3	4½	3 days	52	510	measured 190 estimated 148	3.4	20.2	3.8	76.9	measured 18.3 estimated 14.3	4.6 3.6	26.5 20.6	12.8 9.9	144	92.2
3	Premature; hyperbilirubinemia	4	14	6½ days§	30	560	-- estimated 216	2.6	19.6	4.8	78.2	-- estimated 30.4	-- 6.7	-- 31.0	-- 7.3	102	86.0
4	O-B hemolytic disease	9		33 hr.	52	535	measured 392 estimated 409	1.3	17.6	5.8	58	measured 33.0 estimated 34.5	8.7 9.1	30.0 31.4	5.7 6.0	90	82.0
5	Rh hemolytic disease	5	2	34 hr.	51.5	565	-- estimated 225	2.5	14.4	5.8	63	-- estimated 15.6	-- 6.3	-- 19.7	-- 10.4	126	94.5
6	O-A hemolytic disease	7	12	38 hr.	51	560	-- estimated 350	1.6	20.8	8.0	56	-- estimated 39	-- 17.6	-- 34.0	-- 12.6	87	87.0
7	Premature; hyperbilirubinemia	3	11	4½ days	51	437	measured 176 estimated 168	2.6	19.4	6.2	59.4	measured 16.5 estimated 15.7	9.6 9.2	24.0 23.0	17.1 16.5	105	90.4

* At time of exchange.
† See text.
‡ Using estimated blood volume 100cc. per kilogram, see text.
§ Second exchange transfusion.

in the spinal fluid is more directly related to the protein concentration in the spinal fluid than to the serum bilirubin level. Virtually nothing is known at the present time about the influence of such possible factors as oxygen concentration on the permeability of cell membranes for bilirubin. It is clear, however, from these considerations that without knowledge of all these factors one cannot speak of a critical level of bilirubin in the plasma. This statement is in accord with the common observation that some infants, especially prematures, develop kernicterus at comparatively low plasma levels of bilirubin [12,13] while others seem to tolerate truly extraordinary concentrations without developing demonstrable residues.

The true efficiency of an exchange transfusion as a means of clearing bilirubin cannot be gauged by the residual plasma concentration. The data indicate that the removal of bilirubin accomplished in the course of an exchange transfusion may exceed the amount initially present and should therefore be rated as quite efficient despite the fact that the patient's plasma bilirubin may return to and subsequently remain at levels generally regarded as unsafe. In the cases presented the exchange of red blood cells as judged by the concentrations of fetal hemoglobin amounted to 82%-95%, figures which are in accord with the theoretical expectation for an "adequate" exchange where the removal of vulnerable red cells is the goal.[14] In all cases, however, the exchange as judged by the serum bilirubin levels was seemingly less effective than the red cell exchange (Table, column 11), but, when the movement of bilirubin into the plasma during exchange is allowed for, it becomes apparent that the true efficiency of bilirubin clearance (Table, column 16) in every case was as great as and in most cases greater than that of the red blood cell exchange. This discrepancy is, of course, a reflection of the fact that in the exchange of red blood cells only material in the intravascular compartment is being exchanged, whereas the exchange of bilirubin involves a diffusible substance contained in an additional space several times the size of the plasma volume—namely, the extravascular fluid compartment. By the same token the clearance of bilirubin continues to be effective after the red cell exchange reaches a point of diminishing returns.

It follows that when the removal of bilirubin is the objective the procedure should be carried out slowly in order to take advantage of the equilibrium effect and can be increased in efficiency by increasing the volume used for exchange. Thus Case 2 shows that by using a large volume (ratio of exchange volume to original blood volume 3.4:1) the removal of bilirubin could be increased to 144% of the original value while the removal of red blood cells accomplished at the same time amounted to only 92% of its starting value. By contrast, Case 6, (Table), in which the proportion of exchange to original blood volume was substantially smaller (1.6:1), the removal of red blood cells was almost as good as in Case 2 (87%) but the clearance of bilirubin amounted only to 87% of that contained in the plasma, indicating that clearance of the extracellular compartment was far from complete. Subsequent rebound of the bilirubin concentration beyond the preexchange level in this infant's plasma bears out this interpretation (Fig. 8, Case 6).

In general the correlation between the true efficiency of bilirubin removal as an index of total residual body bilirubin and the presence or absence of the postexchange rebound phenomenon and the maintenance of elevated serum levels was satisfactory. In each case where the removal of bilirubin paralleled that of the red blood cell mass subsequent plasma levels remained low. When a marked divergence between the two curves indicated a substantial extravascular reservoir of bilirubin, there was always a substantial rebound and in most instances levels remained elevated for some

time. In some instances, however, though the rebound was significant it was followed by a rapid decline which may be attributed to rapidly improving hepatic function.

Summary

Examples are given of the variability of the rebound phenomenon with reference to the plasma bilirubin levels after exchange in icteric newborn infants with or without hemolytic disease.

A comparison of the amounts of red blood cells measured as fetal hemoglobin and of bilirubin removed simultaneously throughout exchange transfusion indicated that the reason for the observed variability lies in the existence of an extravascular reservoir of bilirubin. That portion of the reservoir which is contained in the extracellular fluid was shown to be in equilibrium with the plasma bilirubin. It was shown that on removal of plasma bilirubin a gradient from extravascular space into the plasma with rapid transfer of pigment is established and that the plasma bilirubin is replenished from the extravascular reservoir even as it is being removed. It was shown that substantially more bilirubin can be removed than is initially present in the plasma.

The gradient between the extravascular space and plasma can be appraised and furnishes some indication of the size of the extravascular reservoir and more specifically of the degree to which this reservoir has been cleared of bilirubin. It thus affords a better understanding of the true efficiency of exchange transfusion as a method of clearing bilirubin and permits within limits a prediction of subsequent bilirubin levels. This knowledge is of practical value as a guide in determining the necessity of reexchange.

The data indicate that when removal of bilirubin is the purpose of an exchange, greater efficiency can be expected if the procedure is performed slowly and if larger volumes of blood are exchanged than are necessary to bring about an optimal exchange of the red cell mass.

Arguments are presented against the existence of a critical serum bilirubin concentration.

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Progress in Pediatrics

Acute Appendicitis in Infants

Ten-Year Survey at the Los Angeles County Hospital and Report of a Case of Perforated Appendicitis in a Fifteen-Day-Old Infant with Survival

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The reduction in mortality in acute appendicitis during the past 40 years constitutes a remarkable achievement. Unfortunately, there remains a comparatively high death rate in this disease in small infants. Evidence exists that this is due, in part, to a lack of progress in the early diagnosis of this disorder. It appears that the great advances in technical and therapeutic procedures have obscured the importance of early diagnosis. For this reason it seems worth while to review the factors responsible for delay in diagnosis and to discuss some of the associated problems.

This study concerns itself with (a) a report of acute appendicitis with perforation in a 15-day-old infant with survival; (b) an analysis of acute appendicitis in infants 36 months of age or younger, from 1942 to 1952, at the Los Angeles County Hospital, and (c) a survey of the literature.

Acute Appendicitis in a Fifteen-Day-Old Boy

A full-term boy was born on Jan. 27, 1950. During the week preceding his normal delivery, the infant's mother and sister had been ill with moderately severe viral infections. At the age of 15 days, the infant was seen in the office of one of us (M. J. N.) with a history of episodes of restlessness and crying of two days' duration. During the first 36 hours the discomfort was apparently mild and occurred mainly at the time of feedings. At the end of this time, he became increasingly irritable, slept poorly, refused feedings, and for the first time appeared ill. No vomiting had occurred, and the infant had not appeared to be feverish.

Initial examination revealed an acutely ill infant with slightly sunken eyes and a depressed anterior fontanel. The abdomen was markedly distended and generally rigid and tender. No masses were palpable. Peristalsis was diminished. The rectal temperature was 101.8 F.; the white blood count was 7400, with 58% polymorphonuclear cells (30% nonsegmented cells). The infant was admitted to Cedars of Lebanon Hospital the same afternoon. The repeat white blood count was 6100, with 65% polymorphonuclear cells (42% nonsegmented cells), red blood count 5,620,000, and hemoglobin 17 gm. The urine showed no abnormalities. A preoperative diagnosis of peritonitis probably secondary to a perforated appendix was made. Eight hours were required for preoperative preparation, i. e., correction of fluid and electrolyte imbalance, antibiotic therapy, nasogastric suction, and additional consultation.

At surgery (approximately 60 hours after onset), the peritoneal cavity contained a grayish-yellow, cloudy fluid. There was a thick fibrinopurulent exudate in the ileocecal area. The appendix lay free in the right iliac fossa, was acutely inflamed and showed a 2-mm. perforation near its midpoint. An appendectomy was performed and the wound closed without drainage. Culture of the peritoneal exudate grew Escherichia coli and nonhemolytic streptococci. Penicillin was administered for seven days and streptomycin for three days. The infant made an uneventful recovery and was discharged on the eighth postoperative day.

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TABLE 1.—*Ten-Year Survey at the Los Angeles County Hospital of Acute Appendicitis in Infants Three Years or Under*

Case	Age, Sex, Race	Duration of Symptoms	Interval From Adm. to Surg.	Symptoms	Signs	Temp.	WBC and Different.	Adm. Diagnosis	Operative Findings	Procedure	Length of Hosp. Stay	Results	Course	Remarks E.= Enema; L.= Laxative
1	2 yr.; F; Negro	2 days	16 hr.	Fev., vom.; anorexia	Abd. dist.; peristalsis dim.	102 F	19,600; 80% P	Ac. app.	Perf. app.; localized peritonitis	Appy.	27 days	Lived	Wound infection	Sibling died of appendicitis
2	22 mo.; M; Cauc.	5 days	5 hr.	Abd. pain; vomiting	Rigidity RLQ; peristalsis decreased	105.2 F	22,000; 80% P	Perf. app.	Nonperf. mild ac. appendicitis	Appy.	19 days	Lived	Uneventful	E.; associated mesenteric adenitis
3	19 mo.; M	5 days	8 hr.	Vom.; fever; rash; anorexia	Throat injected; RLQ tend., rig.; rash	103.6 F	22,500; 66% P	? Ac. abd.; chic. pox	Perf. app. with abscess	Appy.	38 days	Lived	Wound drained 4 wk.	E. ? mass. preop.; chickenpox; perf. app.
4	16 mo.; F; Negro	6 hr.	8 hr.	Abd. pain; vomiting	Abd. tenderness	104 F	16,000; 80% P	Ac. app. vs. intussusc.	Perf. app.; diffuse peritonitis	Appy.	5 days	Died	High fev.; abd. dist.	L. & E.; died 4th postop. day
5	3 yr.; M; Cauc.	1 day	46 hr.	Abd. pain; vomiting; cough	Abd. dist.; tender RLQ	103.6 F	21,500; 80% P	Tonsil.; ileus	Perf. app.; abscess	Appy.	14 days	Lived	Uneventful	L.; preop. abd. dist.; WBC 26,850; 92% P.
6	2 yr.; M; Cauc.	1 day	15 hr.	Abd. dist.; vomiting	Abd. dist.; gen. tenderness	100.8 F	14,500; 80% P	Ac. abd.	Perf. app. with abscess	Appy.	23 days	Lived	Uneventful	E.
7	2 yr.; F; Cauc.	2 days	5 hr.	Vomiting; Abd. pain; Anorexia	Abd. rig. & dist.	104.2 F	13,800; 87% P	Poss. ac. app.	Perf. app.	Appy.	14 days	Lived	Uneventful	E.; readm. 6 days after disch. with measles
8	2 yr.; M; Cauc.	1 day	3 hr.	Abd. pain; vomiting; dysuria	Abd. rig.; gen. tend.	100.6 F	6,000; 71% P	Poss. ac. app.	Perf. app.	Appy.	7 days	Lived	Uneventful	
9	2 yr.; M; Cauc.	5 days	12 hr.	Fever; anorexia; nausea; diarrhea	Abd. dist.; rigidity	100 F	27,800; 72% P	Poss. ac. abd.	Perf. app.	Appy.	1 day	Died	Asp. vom. at end of op.; Bronchoscope; died on op. table	L. & E.; after anes. mass felt in right lumbar area
10	18 mo.; M; Cauc.	2 days	27 hr.	Fever; vomiting; irrit.	Abd. rig. & dist.	102.6 F	10,300; 75% P	Poss. ac. app.	Ac. gang.	Appy.	20 days	Lived	App. perf. while being delivered; febrile	L.; readm.; ac. intest. obst.; hosp. 16 days & recovered
11	14 mo.; F; Cauc.	19 hr.	50 hr.	Abd. pain; vomiting; diarrhea	Throat inj. 3+ tend. RLQ	103.8 F	12,500; 80% P	Ac. aden.; ac. app.	Nonperf. gangren. app.	Appy.	18 days	Lived	Uneventful	L.; observation, inc. WBC to 17,900

12	20 mo.; F; Cauc.	3 days	16 hr.	Vomiting, fever; abd. pain	Abd. dist. & rigid.	104.4 F	20,000; 90% P	Poss. ac. app.	Perf. app.	Appy.	16 days	Lived	Uneventful	L. & E.
13	2 yr.; M; Cauc.	5 days	8 hr.	Abd. dist.; fever; diarrhea	Abd. dist. & tenderness	101.4 F	10,100; 80% P	Int. obst.; Intussusc.	Perf. app. with peritonitis	Appy.	1 day	Died	P. O. T. rose to 108.8 F & 110 F	L. & E.
14	2 yr.; F; Cauc.	2 days	18 hr.	Abd. pain; vomiting; constipation	Tons. inj. & large; RLQ tend.	101 F	17,500; 80% P	Poss. ac. app.	Perf. app. with peritonitis	Appy.	9 days	Lived	Uneventful	Urine 20 WBC/ HPF on entry.; leukocytes to 23,200 with 82% P
15	2 yr.; M; Cauc.	24 hr.	9 hr.	Abd. dist. & vomit.	"Toxic"; gen. abd. tend. & dist.	103.6 F	12,500; 90% P	Ac. periton.; ? et.	Perf. app. with peritonitis	Appy.	21 days	Lived	Develop. rect. abs.; subside with antibiotics	Adm. chest x-ray; consistent with pneumonia
16	22 mo.; F; Cauc.	5 days	Interval appy.	Abd. pain; vomiting; fever	Tender RLQ mass	103.4 F		Poss. app.			15 days	Lived	Pen.; strep.; nasogas. suction; I.V. fluids; mass disapp.	Interval appy. 3 mo. later
17	23 mo.; M; Cauc.	2 days	20 hr.	Anorexia; abd. pain; vomiting; fever	Irrit.; ENT inj.; diffuse abd. dist.	101.8 F	17,800; 84% P		Perf. app.	Appy.	16 days	Lived	Febrile; purulent drainage from wnd.	
18	2 yr.; F; Cauc.	4 days	12 hr.	Fever; vomiting; abd. dis.	Abd. ten. & dist.	103 F	20,400; 80% P	Poss. intussusc.	Perf. app. with abscess	I. & D.	18 days	Lived	Mass subsided	Interval appy. 4 mo. later
19	22 mo.; M	7 days		Vomiting & diarrhea	RLQ mass; acut. ill; abd. distention	101 F	14,900; 80% P	Poss. app.			23 days	Lived	App. abs. subsided with antibio. & suct. fluids	Did not return for interval appy.
20	2 yr.; M; Cauc.	4 hr.	7 hr.	Abd. pain; vomiting	Diff. abd. tend. & dist.	101.4 F	15,700; 93% P	Poss. ac. app.	Perf. app. with abscess	Appy.	8 days	Lived	Uneventful	Similar episode 1 mo. before entry, subsided with pen.
21	2 yr.; M; Cauc.	1 day		Fever; abd. pain; nausea; convul.	Mod. tend. RLQ mass 2 days later	103 F	17,500; 85% P				16 days	Lived	Conser. Rx; afebrile in 1 wk.; mass disapp.	L.; interval appy. 3 ½ mo. later with recov.
22	2 yr.; F; Cauc.	5 days	4 hr.	Fever; cough; abd. pain; vomiting	Abd. rig. & distention	102.6 F	12,300; 72% P		Autopsy; perf. app. with peritonitis		1 day	Died	Shock fol. anes.; resuscitation failed	E.; died on op. table.; no surg.
23	2 yr.; F; Cauc.	7 days	10 days	Anorexia; fever; abd. pain	Abd. dist.; tender. RLQ mass	102 F	12,300; 86% P	Tonsillitis	Perf. app. with abscess	I. & D.	34 days	Lived	Conserv. Rx. for 10 days & then op.	E.; did not return for interval appy.
24	2 yr.; M; Negro	3 days	17 days	Cold; anorexia; vomiting	ENT fiery red.; mod. abd. dist. & tend.	103.8 F	7,500; 60% P		Perf. app.; periton.; intest. obst.	Appy.	34 days	Lived	Prog. abd. dist.; mass 3 days lat.; cons. Rx.; op. for obst.	Seen as out-pt. 1 day before entry & sent home as "cold" E. (in hosp.)

TABLE 1.—*Ten-Year Survey at the Los Angeles County Hospital of Acute Appendicitis in Infants Three Years or Under*—Continued

Case	Age, Sex, Race	Duration of Symptoms	Interval From Adm. to Surg.	Symptoms	Signs	Temp.	WBC and Different	Adm. Diagnosis	Operative Findings	Procedure	Length of Hosp. Stay	Results	Course	Remarks E. = Enema; L. = Laxative
25	14 mo.; M; Negro	2 days	32 hr.	Anorexia; vomiting; "colic"	Abd. tend. & dist.	104.8 F	10,900; 40% P	URI; Gastroent.	Perf. app. with peritonitis	Appy.	15 days	Lived	Febrile course for 10 days then improved	E.; 29 hr. after entry WBC rose to 17,000 with 80% P
26	2 yr.; F; Cauc.	15 hr.	11 hr.	Abd. pain; anorexia; fever	Mod. abd. dist.	104 F	15,000; 76% P		Perf. app.	Appy.	18 days	Lived	Dev. URI on 10th P. O. day; grad. improv.	E.; urine 4 to 10 WBC/HPF with clumps
27	2 yr.; F; Negro	7 days	8 hr.	"Cold"; vomiting; diarrhea	Abd. dist. diffuse tend.	103.2 F	6,300; 76% P	Tonsil.; pharyng.	Perf. app. with periton.	Appy.	13 days	Lived	Grad. impr.	Given pen. prior to entry for tonsillopharyngitis
28	2 yr.; F; Negro	3 days	3 hr.	Abd. pain; vomiting	Abd. tend. & rigid.; RLQ mass	104 F	8,900		Perf. app.	Appy.	28 days	Lived	Grad. impr.	E.
29	2 yr.; F; Cauc.	1 days	10 hr.	Abd. pain; fever	Abd. tend. and dist.	104.4 F	13,000		Ac. gang.; no perf. appendix	Appy.	12 days	Lived	Grad. impr.	Chest x-ray on entry consistent with pneumonia or URI
30	2 yr.; M; Cauc.	36 hr.	6 hr.	Abd. cramps; fever; no vom.	Throat red; Abd. tend.	104.4 F	12,200; 75% P	Poss. app.	Nonperf. ac. gang. app.	Appy.	13 days	Lived	Grad. impr.	"Cold" 2 wk. before entry
31	19 mo.; M; Cauc.	6 days	In hosp.	Nausea; vomiting; abd. dist.	Abd. dist. & quiet		37,600; 66% P		Perf. app. with abscess	I. & D.	52 days	Lived	Wnd. drained many wk.; refer to pvt. MD for interval appy.	In hosp. with typhoid fever; blood cult. for pos. S. typh.
32	2 yr.; M; Cauc.	3 days	15 hr.	Fever; vomiting; diarrhea; abd. pain	Abd. dist.; diffuse tend.		7,600; 76% P	Meas.; poss. ac. app.	Perf. app. with peritonitis	Appy.	8 days	Lived	Uneventful	In hosp. with meas.; peritonitis; culture—strep. vir. & E. coli

33	18 mo.; F; Cauc.	36 hr.	6 hr.	Vomiting; constip.; fever	Abd. dist. & rigid.	101.8 F	13,200; 80% P		Nonperf. ac. supp. app.	Appy.	12 days	Lived	Uneventful	E.; urine 5 to 10 WBC/HPF
34	1 yr.; F; Cauc.	2 days	6 hr.	Abd. pain & vomit.	Abd. tend. & dist.	102 F	18,600; 80% P	Poss. ac. app.	Perf. app. with peritonitis	Appy.	16 days	Lived	Gradually improved	
35	11 mo.; F; Cauc.	2 days	3 hr.	Abd. pain; vomiting	Abd. dist.; gen. tend.	100.2 F	17,700; 88% P	Ac. app.; Ac. ent.	Nonperf. ac. gang. app.	Appy.	6 days	Lived	Uneventful	
36	2 yr.; M; Cauc.	4 days	16 hr.	Cough; fever; abd. pain; vomiting	Abd. rig. & tend.; throat inj.	105 F	14,900; 92% P	Pneu. vs. ac. app.	Perf. app. With periton.	Appy.	13 days	Lived	Grad. impr.	E.
37	2 yr.; M; Cauc.	36 hr.	3 hr.	Abd. pain; vomiting	Abd. rig. & tend.	101.4 F	21,900		Perf. app. with abscess	Appy.	9 days	Lived	Uneventful	
38	3 days; F		7 days	Vom.; abd. dist.; diarrhea; cyanosis	Abd. dist.; acutely ill		6,600; 48% P	Infectious diarrhea	Perf. base of app. with peritonitis	Closure perf.	7 days	Died	Shock postop.; Died 5 ½ hr. postop.	Trans. from another hosp. on 3rd day of life.; 7th hosp. day noted abd. dist. vom. and cyan.

Ten-Year Survey at Los Angeles County Hospital

Our experience with this patient prompted us to review all of the cases of acute appendicitis in infants, 36 months of age or younger, at the Los Angeles County Hospital during the 10-year period from 1942 to 1952 (Table 1). Cases in which the appendix was involved secondarily, as in incarcerated hernia or intussusception, were not included.

There were 38 cases of primary acute appendicitis, with five deaths, a mortality of 13.2%. Perforations occurred in 31 infants, an incidence of 81.6%. There were eight infants who had an appendiceal abscess, either having it at the time of entry to the hospital or developing a mass while under observation in the hospital. There was no mortality in this group.

Coexisting Disease

In the entire group of 38 cases there were 14 infants who were admitted to the hospital with one of the following coexisting diseases: measles, chickenpox, typhoid fever, acute tonsillitis, nasopharyngitis, and acute gastroenteritis. The presence of acute appendicitis was not suspected at the time of admission in 8 of the 14 cases. The additional diagnosis of an acute surgical abdomen and the operation in these 14 cases were delayed from 6 hours to 17 days after entry. One infant with a 7-day delay had an initial diagnosis of acute gastroenteritis and succumbed five and one-half hours after surgery (Case 38; Fatal Cases). Three cases with coexisting diseases are presented in more detail as illustrations of delay in diagnosis.

Case 31.—A 19-month-old infant was admitted to the Communicable Disease Unit with a proved case of typhoid fever. On the 26th hospital day he became irritable, febrile, refused food, and vomited his dinner. On the following day he developed abdominal distention which became more marked during the next four days. The white blood count increased from 9100 (70% polymorphonuclear cells) to 43,000 (88% polyporphonuclear cells). On the fifth day after the onset of abdominal symptoms, a large right lower quadrant mass was palpable. Exploratory operation was performed and an appendiceal abscess was found and drained. After a prolonged convalescence the infant was discharged and referred to his private physician for an interval appendectomy.

Case 3.—A 19-month-old infant was admitted to the Communicable Disease Unit with a history of vomiting, anorexia, and fever of 5 days' duration. Two days before entry he developed a rash and a diagnosis of chickenpox was made. Repeated enemas had been administered for constipation. He was seen early in the course of his illness by two physicians, but it was not until the fifth day that an acute surgical abdomen was suspected and hospitalization was advised. On admission, the infant had chickenpox and signs of acute peritonitis. It was felt that the peritonitis was secondary either to acute appendicitis or to intussusception. The white blood cell count was 22,500 with 66% polymorphonuclear cells and many stab forms. At surgery, a gangrenous appendix with perforation was found and an appendectomy performed. The wound drained for four weeks. The infant was discharged fully recovered.

Case 32.—A 2-year-old infant was admitted to the hospital with measles and a history of fever, vomiting, diarrhea, and abdominal pain of 3 days' duration. On admission, the abdomen was slightly distended and diffusely tender. The white blood cell count was 7600 with 76% polymorphonuclear cells. The surgical resident advised further observation. The surgical consultant, who examined the infant 12 hours later, suggested the possibility of acute appendicitis or "necrosis of the bowel" and advised immediate surgery. At surgery, 15 hours after admission, acute appendicitis with perforation and peritonitis was found. Appendectomy was performed and the infant made an uneventful recovery.

*Comments.**—The diagnosis of acute appendicitis in an infant with a coexisting disease often represents an extremely difficult problem. In 100 consecutive cases in which the appendix was examined in children under 12 years of age at the Haynes Memorial Hospital,[107] Infectious Disease Unit, Boston, 96 patients (96%) demonstrated some stage of appendicitis and in 61 of these, the appendix had perforated. Eighty-eight of these children actually had

* The other cases with coexisting disease are numbers 5, 11, 14, 17, 23, 24, 25, 27, 30, 36, and 38 in Table 1.

a coexisting infectious disease, and the remaining 12 had been exposed to or were thought to be in the prodromal stage at the time of admission. Seventy-seven of the eighty-eight cases were accounted for by scarlet fever, measles, and chickenpox. In a comparable group of patients without coexisting disease from the Children's Hospital in Boston, the perforation rate was 44.8%. In our series, the 14 cases with coexisting disease under 3 years of age, perforation occurred in 12 infants, an incidence of 86%. In the remaining 24 cases without associated disease, perforations occurred in 79%. Twenty out of twenty-one infants without coexisting disease were operated upon in less than 24 hours following hospitalization (95%). Only 7 out of 14 cases with coexisting disease were operated upon within 24 hours following admission (50%). Even more striking is the fact that 15 out of the 21 cases without coexisting disease were operated on within 12 hours (71%), but only 3 out of 14 cases with coexisting disease (21%) were operated on in the first 12 hours. Although our figures may not be statistically significant, the probability remains that in the presence of a coexisting disease the diagnosis of associated acute appendicitis may be delayed.

Conservative Management of Appendiceal Abscesses

There were eight infants in our series who had a well-localized appendiceal abscess of whom five were treated conservatively. The initial treatment, hospital course, and eventual outcome in these five cases are of sufficient interest to warrant more detailed presentation.†

CASE 16.—A 22-month-old girl was admitted to the hospital with a history of fever, abdominal pain, and vomiting of 5 days' duration. The patient had been given an enema on the second day of illness. The rectal temperature on entry was 103.4 F. A tender mass was present in the right lower quadrant, and a diagnosis of appendiceal abscess was made. Therapy consisted of penicillin, streptomycin, intravenous fluids, and nasogastric suction. The mass gradually disappeared, and the infant was discharged on the 15th hospital day. She returned three months later for an interval appendectomy and made an uneventful recovery.

CASE 19.—A 22-month-old boy was admitted to the hospital with a history of vomiting and diarrhea of 7 days' duration. On the advice of a physician, an enema had been administered on the first day of illness. The admission temperature was 101 F.; white blood cell count was 14,900, with 80% polymorphonuclear cells. A mass was palpable in the right lower quadrant, and a diagnosis of appendiceal abscess was made. On conservative treatment with antibiotics, nasogastric suction, and intravenous fluids, the mass resolved and the infant was discharged on the 23rd hospital day. The patient did not return for interval appendectomy.

CASE 23.—A 2-year-old girl was admitted to the hospital with a history of fever, anorexia, abdominal pain, and constipation of 7 days' duration. Magnesia magma (milk of magnesia) and liquid petrolatum emulsion (mineral oil) had been given on the first day of illness and several enemas three or four days later. The admission temperature was 102 F.; the white blood cell count was 12,350, with 86% polymorphonuclear cells. There was generalized abdominal tenderness and distention, and a 3 by 4-cm. mass was palpable in the right lower quadrant. A diagnosis of perforated appendicitis with localized abscess was made and the patient treated conservatively with antibiotics, nasogastric suction, and parenteral fluids for 10 days. The abdominal manifestations progressed in intensity and the mass appeared to be enlarging. At surgery, on the 10th hospital day, incision and drainage of a large abscess in the right iliac fossa was performed and about one pint of pus evacuated. The patient improved and was discharged in satisfactory condition on the 34th hospital day. She did not return for interval appendectomy.

CASE 24.—A 2-year-old Negro boy was admitted to the hospital with a history of upper respiratory symptoms, anorexia, and vomiting of 3 days' duration. The admission temperature was 103.8 F.; the white blood cell count was 7500 with 60% polymorphonuclear cells. The throat and both tympanic membranes were moderately injected. The abdomen was diffusely tender and moderately distended. The surgical consultant who saw the infant shortly after entry made a diagnosis of probable ileus secondary to an upper respiratory infection and advised observation. On the third hospital day the white blood cell count rose to 17,000, with 99% polymorphonuclear cells. At this time, the surgical consultant made a diagnosis of generalized peritonitis, probably secondary to a perforated appendix, and advised conservative

† The three other cases were numbers 18, 28, and 31.

therapy. Penicillin, streptomycin, nasogastric suction, and intravenous fluids and blood were administered. However, signs and symptoms of acute intestinal obstruction developed, and the infant was taken to surgery on the 17th hospital day. At operation, there was acute intestinal obstruction due to an inflammatory band, secondary to a perforated inflamed appendix. Appendectomy and lysis of the obstructive bands were performed. The patient had an uneventful recovery and was discharged on the 34th hospital day.

CASE 21.—A 2-year-old boy entered the hospital because of fever, convulsions, anorexia, and abdominal pain of one day's duration. The temperature was 103 F. Rigidity and moderate tenderness were present in the right lower quadrant. The white blood cell count was 17,500, with 85% polymorphonuclear cells. Two days after entry a right-lower-quadrant mass was diagnosed as an appendiceal abscess, and the patient was treated conservatively. The fever subsided in one week, and the mass gradually disappeared. The patient was discharged on the 16th hospital day. An interval appendectomy was performed three and one-half months later with an uneventful recovery.

Comments.—One case failed to return for an interval appendectomy, and no additional information is available. Two patients returned for interval appendectomy and made uneventful recoveries. In the remaining two patients, a conservative course was initially planned, but surgery was performed on the 17th and 10th hospital days, respectively, because of the development of an acute intestinal obstruction in one and a progressively enlarging abscess in the other.‡

This group of cases, though small, serves to confirm the prevailing opinion that conservative treatment, except in the presence of an unusually severe coexisting disease, should probably be abandoned. It should also be emphasized that there are no criteria available to determine the duration of antibiotic therapy necessary to eradicate the infection and prevent a relapse. This difficulty is illustrated by Riley's [151] report of acute appendicitis in a patient in whom all signs and symptoms of the disease disappeared on drug therapy, but at surgery on the fourth day of illness an acutely inflamed appendix was found.

‡ The latter case likewise failed to return for interval appendectomy.

Fatal Cases

There were five deaths in this series, a mortality of 13.2%. During the same period, from 1942 to 1952, at the Los Angeles County Hospital, there were 5354 operations performed for acute appendicitis as the primary disease. The over-all mortality in the latter group (comprising all ages) was 1.2%. The mortality in the first five-year period (1942 to 1947) was 1.6%, and in the last five-year period (1947 to 1952) the mortality was 0.8%. The mortality from acute appendicitis in infants 3 years or younger was 11 times greater than in the group comprising all ages.

The five deaths were of sufficient interest to warrant a more detailed presentation.

CASE 4.—A 16-month-old Negro girl was admitted to the hospital with a history of vomiting, abdominal pain, and fever of 6 hours' duration. Milk of magnesia and an enema had been administered on the advice of the attending physician. Vomiting persisted and the infant was referred to the hospital with a diagnosis of probable food poisoning. On entry, the infant appeared acutely ill and moderately lethargic. The temperature was 104 F, pulse rate 180, and respirations 62. The abdomen was diffusely tender on palpation. The hemoglobin was 43% and the white blood cell count 9500 with 56% polymorphonuclear cells. No sickled red blood cells were observed. Urinalysis was normal. The surgical consultant who examined the infant shortly after admission did not feel that the patient had a surgical condition and advised close observation. Approximately four hours after admission, the white blood cell count rose to 16,000, with 80% polymorphonuclear cells. Reexamination at this time by the surgical consultant suggested the possibilities of appendicitis or intussusception, and surgery was advised. At surgery (eight hours after entry), an acutely inflamed appendix with a perforation at its base and generalized peritonitis were found. Appendectomy was performed, the stump not being inverted, and 1 gm. of sulfanilamide crystals was placed in the peritoneal cavity. Postoperative therapy consisted of oxygen, nasogastric suction, blood transfusions, and intravenous sodium sulfathiazole. The patient's course was one of high fever associated with marked tachycardia. The abdominal distention progressively increased, and for this complication neostigmine (Prostigmin) was used

on the second postoperative day. Extreme toxicity persisted and the infant died on the third postoperative day. Autopsy was not obtained.

Comment.—The clinical course of this illness strongly suggests the possibility of an unreliable history and a considerable delay in diagnosis. The patient was seen in 1943, and the limitations in our knowledge of preoperative treatment and chemotherapy are obvious. The use of neostigmine seems ill-advised.

CASE 9.—A 2-year-old boy was admitted to the hospital with a history of fever and anorexia of 5 days' duration. Diarrhea and abdominal pain subsequently developed. Three days before entry magnesia magma was administered, and on the next day an enema was given. On entry the patient appeared to be acutely ill. The temperature was 100 F; the white blood cell count was 27,800, with 72% polymorphonuclear cells (28% nonsegmented cells). There was moderate generalized abdominal distention and marked rigidity and tenderness along the right rectus muscle. No masses were palpable, and peristalsis was diminished. Under anesthesia (12 hours after entry to the hospital), a mass could be felt in the right lumbar area. At exploration, this mass consisted of a perforated appendix with adherent viscera and omentum. Appendectomy was performed. The anesthesia was deepened just prior to closure of the peritoneum, but unfortunately vomiting and aspiration occurred. Bronchoscopic aspiration was temporarily beneficial, but death occurred at the conclusion of the operation.

Comment.—Failure to use continuous gastric lavage prior to surgery plus avoidable anesthetic difficulties were probably responsible for the accident of aspiration. In retrospect, this would appear to be a preventable death, although the five-day delay in diagnosis was primarily responsible for the child's poor condition.

CASE 13.—A 2-year-old boy was admitted to the hospital with a history of fever, diarrhea, and abdominal pain of 5 days' duration. Magnesia magma had been administered. On the day prior to entry, the attending physician noted that the abdomen was distended and advised an enema. Following the enema, the abdominal distention increased, and because of the possibility of an intestinal obstruction, hospitalization was advised. On entry, the child appeared acutely ill; the temperature was 101.4 F. The abdomen was markedly distended, rigid, and tender. Peristalsis was greatly diminished. The white blood cell count was 10,150 with 80% polymorphonuclear cells. Surgery was performed eight hours after admission. A McBurney incision was made, and upon opening the peritoneal cavity a great quantity of thin yellow pus escaped under pressure. A large perforation in the distal third of the appendix and generalized peritonitis were present. Appendectomy was performed. Two grams of sulfanilamide crystals were placed in the peritoneal cavity, and a large Penrose rubber drain was brought out from the base of the cecum. Blood, plasma, intravenous fluids, oxygen, and intravenous and intramuscular penicillin were administered. Depite all supportive measures the child's temperature rose to 108.8 F, and terminally to 110 F. Death occurred six hours postoperatively.

Comment.—There is little doubt that the five-day delay in diagnosis and the presence of generalized peritonitis were the major factors responsible for this child's death. This case does illustrate the importance of repeated examinations of the patient during the preoperative period in order to select the optimum time for operation. It was difficult to obtain adequate information from the history in respect to this point.

CASE 22.—A 2-year-old infant was admitted to the hospital with a history of cough, nasal discharge, and a low-grade fever beginning five days prior to entry. Twenty-four hours after the onset of these symptoms, the child first complained of abdominal pain and an enema was administered. Vomiting did not occur until the fifth day of the illness, and at this time abdominal distention was first noted. The child was then seen by a physician who prescribed an enema, and, although this procedure decreased the abdominal distention, hospitalization was advised. On entry, the child appeared acutely ill. The temperature was 102.6 F. On abdominal examination, there was marked distention, tympany, generalized rigidity, and markedly diminished peristalsis. No mass was palpable. The white blood cell count was 12,300, with 72% polymorphonuclear cells. The urine had a specific gravity of 1.030, a trace of albumin and acetone, and numerous hyaline and granular casts. The blood nonprotein nitrogen was 35 mg. per 100 cc. and the CO_2 34 vol.%. Preoperatively, the child was given 5% dextrose in normal saline intravenously, 200,000 units of penicillin, and 0.25 gm. of streptomycin intramuscularly. Anesthesia (open drop vinyl ether [Vinethene] followed by ether) was started five and one-half hours after entry. Following the start of anesthesia the child's condition became critical, and despite the administration of caffeine and epinephrine (Adrenalin), she died before surgery was performed.

On postmortem examination, a thickened, opaque, and markedly injected peritoneum was present. The peritoneal cavity contained 30 to 40 cc. of free yellowish-white purulent material. The intestinal loops were markedly distended and covered in the right lower quadrant by a fibrinous exudate. The appendix was gangrenous and had a small perforation in its distal third. Autopsy diagnoses: Suppurative peritonitis due to acute gangrenous appendicitis with perforation.

Comment.—It seems likely that the initial diagnosis was delayed because of a coexisting upper respiratory infection and the late onset of vomiting. The preoperative treatment was woefully inadequate according to present standards, and full efforts to prevent and combat shock were lacking. In view of the duration of the illness and the condition of the patient, proper preparation for surgery would ordinarily have required a longer time.

CASE 38.—A 3-day-old girl was admitted to the hospital with the diagnosis of acute enteritis. The infant was delivered in another hospital. On the second day of life, she developed vomiting and diarrhea associated with listlessness and lack of interest in feeding. Her admission temperature was 100.8 F. The abdomen was soft, no masses were palpable, and peristalsis was active. Parenteral fluids and chloramphenicol (Chloromycetin) were administered. The course was thought to be satisfactory until vomiting and abdominal distention developed at 10 days of age. The vomitus had a fecal odor. A diagnosis of upper intestinal obstruction was made and the abdomen explored. The cecum and terminal ileum were covered with a plastic exudate. A minute perforation in the cecal wall and base of the appendix was identified. The operative report stated that "the appendix was not primarily inflamed although it was somewhat thickened at its base." The peritoneum was moderately inflamed and many intestinal loops were greatly distended. No evidence of obstruction was found. The perforation was closed and 1 gm. of streptomycin and 200,000 units of penicillin were placed in the peritoneal cavity. The infant died five and one-half hours postoperatively.

Comment.—There is uncertainty as to whether this case represents a gastroenteritis of the newborn with secondary perforation of the cecum at the base of the appendix or an unrecognized primary appendicitis with subsequent perforation and generalized peritonitis. In the absence of other cases of diarrhea in the nursery, it is difficult to postulate the presence of epidemic diarrhea of the newborn. This information was not recorded on the history. Any unexplained case of diarrhea in a newborn infant warrants frequent examination in order to exclude other causes. There seems little doubt that the symptoms of appendicitis were masked by noncurative doses of chloramphenicol until the signs of peritonitis finally became obvious.

Survey of Statistics

The high incidence of perforation (81.6%) and the high mortality rate (13.2%) in our series of 38 infants compared to the adult group in the same hospital during the identical period prompted us to survey some of the literature in order to ascertain if any progress in the earlier recognition of the disease in infants has been made during the last few decades. The improvement in the early diagnosis of acute appendicitis is demonstrated in Table 2, *A*. Comparable improvement, however, has not occurred in infants (Table 2, *B*). In a group of 296 patients 4 years of age or less, reported by Green and Watkins[77] during the years from 1930 to 1941, there were 35.2% not operated on until 3 or more days after the onset of illness. In 159 infants 2 years of age or less, observed in three insti-

TABLE 2.—*Distribution of Cases of Acute Appendicitis in Relationship to Time Interval from Onset of Symptoms to Surgery*

	Operation Performed Within:		
A. Cases Reported from Sweden—All Ages (Nyström)[184]			
Year	24 Hours	48 Hours	72 Hours or more
1888-1902	4%	12%	74%
1903	16%	32%	42%
1917	44%	65%	19%
1930	59%	76%	16%
1934	71%	85%	7%
B. 296 Infants 4 Years of Age or Under (Green and Watkins)[77]			
1930-1941	8.1%	40.5%	35.2%
C. 159 Infants 2 Years of Age or Under (Combined Series)*			
1940-1952	21.4%	42.1%	36.5%

* References 18 and 56 and authors' series.

TABLE 3.—*Perforation Rate*

Age in Years	Before 1930		1930-1940		After 1940	
	No. Pts.	% Perf.	No. Pts.	% Perf.	No. Pts.	% Perf.
5-16	4183 (a)	38.2	6860 (b)	29.1	2328 (c)	20.5
Under 5	692 (d)	65.9	670 (e)	63.4	151 (f)	53.5
" 4	70 (g)	88.5	353 (h)	78.8	406 (i)	68.2
" 3	31 (j)	83.9	100 (k)	81.2	182 (l)	78.0
" 2	25 (m)	84.0	95 (n)	84.3	132 (o)	81.8

a. References 22, 59, 66, 86, 102, 104, 108, 113, 143, 144, 145, 175, 188.
b. References 3, 45, 54, 77, 95, 96, 116, 173, 176, 188.
c. References 55, 56, 81, 114, 119, 137, 157, 170, 182.
d. References 15, 16, 22, 59, 103, 113, 143, 144, 145, 186.
e. References 3, 60, 77, 88, 159, 173.
f. References 36, 119, 137, 170.
g. References 16, 103, 144.
h. References 3, 34, 54, 60, 64, 95, 150, 173.
i. References 36, 55, 81, 114, 119, 157, 171.
j. References 16, 103, 144.
k. References 3, 7, 60, 64, 159, 173.
l. References 36, 56, 84, 114, 119, 182, and the authors' series.
m. References 2, 16, 22, 101, 144, 161, 175.
n. References 3, 7, 18, 60, 64, 88, 95, 159, 161.
o. References 18, 36, 78, 81, 114, 157, and the authors' series.

tutions during the following decade, 36.5% were not operated until 3 or more days after the onset of illness. In a group of 31 infants under 12 months of age, collected from our cases and miscellaneous case reports, [20,23,44,51,59,63,75,78,79,88,106,109,112,120,121,127,132,149,153,156,157,159,161,162,177,185] 58% were not operated on until 3 days or more after the onset of illness. Although these represent mixed groups reported by various authors, the implication that little or no progress has been made in early diagnosis in infants seems evident.

Another approach in determining progress in the early recognition of appendicitis is by a statistical comparison of the perforation rate in succeeding decades. Table 3 represents the combined perforation rate in patients under 16 years of age collected mainly from the English literature. It is apparent that the perforation rate has diminished from 38.2% to 20.5% in children between 5 and 16 years of age. In the group under 5 years of age, no significant improvement is apparent and in very young infants the rate has remained essentially unchanged.

Table 4 provides evidence that the perforation rate in infants is considerably higher than in adults even when seen within the first 24 hours of illness. Although the number of cases is small and the figures remain questionable because of the difficulties in determining the exact time of onset of the illness, they do suggest that a far greater effort in early diagnosis is necessary in young children if operation is to be performed before perforation occurs.

TABLE 4.—*Perforation Rates in Relationship to Time Interval from Onset of Symptoms to Surgery*

Hours	All Ages(a)		0-4 Years(b)	
	No. Pts.	% Perf.	No. Pts.	% Perf.
0-24	12,357	7.5%	37	70.2%
24-48	13,630	17.2%	52	76.9%
48-72	4,686	34.0%	51	92.1%
Over 72	6,405	46.8%	90	90.0%

a. References 29, 77.
b. References 56, 88, 159; authors' series.

TABLE 5.—*Mortality as Related to Appendiceal Perforation in Children Five Years or Under*

Year	With Abscess		With Peritonitis	
	No. Pts.	% Mort.	No. Pts.	% Mort.
Before 1930(a)	93	5.4%	130	41.5%
1930-1940(b)	245	6.9%	305	26.9%
After 1940(c)	101	3.0%	97	19.6%

a. References 2, 16, 59, 103, 113, 144, 175.
b. References 60, 77, 88, 95, 96, 159, 184.
c. References 18, 55, 56, 84, 137, 170; authors' series.

Table 5 illustrates the comparative mortality in perforated cases in children 5 years or under. A marked reduction in the mortality from peritonitis has occurred since

TABLE 6.—*Acute Appendicitis—First Year of Life*

Age, Mo.	No. Pts.	Reference	Non-Perf.	Perforations			Surgery		Results	
				Perf.	Absc.	Perit.	Yes	No	Lived	Died
Before 1930										
0-2	20	(a)	1	13	2	0	4	9	3	13
3-5	9	(b)	2	5	3	1	4	4	2	6
6-8	12	(c)	4	2	1	1	5	1	6	1
9-11	10	(d)	2	7	1	0	5	2	4	4
No stated Age	50	(e)								
Total	101			27		17	18	16	15	24
Per Cent				75%			53%			61.6%
1930-1940										
0-2	6	(f)	0	6	2	4	2	6	1	5
3-5	5	(g)	1	3	0	3	3	1	2	3
6-8	4	(h)	1	3	2	1	4	0	4	0
9-11	9	(i)	1	3	..	2	4	..	4	2
No stated Age	7	(j)	..	2	1	1	..	..	6	1
Total	31		3	17		11	13	7	17	11
Per Cent				85%			65%			39.3%
After 1940										
0-2	13	(k)	4	5	2	3	7	4	4	7
3-5	3	(l)	..	2	2	..	2	..	3	0
6-8	4	(m)	2	1	..	..	..	1	3	1
9-11	6	(n)	3	1	..	1	4	..	5	..
No stated Age	10	(o)	2	4	..	..	..	..	5	..
Total	36		11	13	4	4	13	5	20	8
Per Cent				54.2%			72.2%			28.6%

a. References 2, 19, 48, 51, 74, 89, 93, 100, 139, 160.
b. References 2, 80, 85, 113, 162.
c. References 2, 21, 50, 69, 75, 98, 100, 109, 112, 153, 156.
d. References 2, 59, 88, 109, 168.
e. References 2, 39, 101, 167, 187.
f. References 5, 40, 98, 106, 159, 161.
g. References 41, 44, 117, 161.
h. References 79, 94, 112, 177.
i. References 5, 20, 52, 64, 127, 132, 146, 154, 161.
j. References 77, 95, 184.
k. References 9, 18, 49, 105, 120, 121, 124, 140, 169, 185; authors' series.
l. References 23, 63, 84.
m. References 17, 18, 110.
n. References 18, 78, 150, 157; authors' series.
o. References 1, 9, 36, 56, 81.

1930. Significantly, however, when appendiceal perforation resulted in abscess formation, the mortality was 3% compared with 19.6% in cases with generalized peritonitis. Cantrell and Stafford[38] reporting on the diminishing mortality from appendicitis noted that there were no deaths in their patients with appendiceal abscess, although this group constituted 44% of the perforations.

Data were obtainable in 118 cases of acute appendicitis in infants in the first year of life. Because of the lack of uniformity in these reports, many details necessary for complete analysis were not available. The number of cases are too few to permit a critical analysis of the results in the three periods reviewed. Certain trends, however, are apparent. Information concerning mortality was available in 95 cases (Table 6). The mortality rate in this group comprising the first 12 months of life has decreased from 61.6% to 28.6%. However, within the same group the mortality in the first six months of life still remains appallingly high (50%). The youngest case on record with recovery following surgery is a 10-day-old premature infant reported by Meigher and Lucas.[120]

The greater rapidity of appendiceal perforation in infants as compared with that in adults has been generally accepted. However, the ability of infants to localize an appendiceal infection has not been suffi-

TABLE 7.—*Mortality Rates in Various Age Groups*

Age in Years	Before 1930		1930-1940		After 1940	
	No. Pts.	% Mort.	No. Pts.	% Mort.	No. Pts.	% Mort.
All Ages	74,432 (a)	5.2%	66,786 (b)	3.7%	88,124 (c)	1.0%
Under 16	16,153 (d)	7.5%	23,696 (e)	4.1%	10,317 (f)	1.3%
Under 5	1,290 (g)	23.5%	981 (h)	12.2%	226 (i)	2.7%
Under 4	92 (j)	23.9%	613 (k)	14.3%	234 (l)	7.3%
Under 3	48 (m)	39.6%	315 (n)	21.2%	195 (o)	6.7%
Under 2	67 (p)	47.8%	159 (q)	33.9%	128 (r)	10.2%
Under 1	39 (s)	61.6%	28 (t)	39.3%	28 (u)	28.6%

a. References 10, 11, 14, 24, 25, 47, 52, 62, 68, 69, 82, 83, 91, 104, 108, 111, 115, 126, 128, 130, 141, 146, 160, 164, 165, 179, 180, 181, 183, 188.
b. References 17, 25, 28, 29, 31, 67, 72, 77, 84, 92, 94, 97, 118, 132, 147, 152, 174.
c. References 30, 31, 61, 65, 82, 84.
d. References 4, 10, 11, 13, 15, 21, 22, 24, 26, 27, 33, 47, 52, 53, 55, 57, 58, 59, 62, 64, 66, 70, 76, 83, 86, 91, 101, 102, 103, 104, 108, 111, 113, 115, 116, 125, 126, 128, 130, 131, 133, 134, 136, 141, 143, 144, 158, 160, 163, 166, 172, 175, 178, 181, 185, 188.
e. References 1, 3, 7, 8, 18, 28, 29, 32, 34, 35, 37, 41, 45, 46, 54, 60, 64, 73, 77, 87, 92, 95, 96, 97, 99, 118, 122, 123, 134, 134, 136, 140, 142, 144, 145, 146, 147, 164, 173.
f. References 1, 30, 32, 36, 55, 56, 65, 71, 78, 81, 82, 84, 90, 114, 119, 129, 134, 137, 148, 150, 157, 170, 171, 174, 182.
g. References 16, 22, 42, 43, 52, 58, 59, 62, 66, 102, 103, 113, 115, 144, 166, 172, 178, 181, 183, 188.
h. References 1, 3, 6, 35, 60, 77, 87, 88, 147, 159, 173.
i. References 1, 36, 90, 119, 129, 137, 170.
j. References 16, 42, 65, 102, 103, 166.
k. References 3, 32, 34, 54, 60, 64, 77, 88, 95, 159, 173.
l. References 36, 55, 78, 90, 114, 119, 129, 157.
m. References 10, 16, 42, 66, 102, 103, 166, 178.
n. References 3, 7, 32, 60, 64, 77, 87, 88, 159, 173.
o. References 36, 56, 84, 90, 114, 119, 129, 182; authors' series.
p. References 2, 15, 16, 22, 42, 58, 66, 102, 109, 161, 175.
q. References 1, 3, 7, 18, 32, 37, 60, 77, 88, 95, 159, 161.
r. References 18, 39, 78, 90, 114, 129, 157, 161; authors' series.
s. References 2, 19, 21, 39, 48, 50, 51, 59, 75, 80, 85, 88, 89, 93, 109, 113, 139, 153, 156, 160, 162, 167.
t. References 5, 20, 40, 41, 44, 77, 79, 94, 95, 98, 106, 112, 117, 127, 132, 146, 159, 161, 177, 184.
u. References 9, 17, 18, 19, 21, 23, 36, 49, 63, 81, 84, 105, 120, 121, 124, 149, 150, 157, 185; authors' series.

ciently emphasized. Information available on 48 infants under one year of age (Table 6) who had perforated appendicitis revealed that peritonitis was present in 32 patients and that in the remaining 16 a localized appendiceal abscess was present. It is also significant that the incidence of surgery for acute appendicitis in infants in the first year of life (in the above group of 118 cases) has increased from 53% to 72.2%.

Table 7 shows the decreasing mortality rates in all ages in the past three decades. It is noteworthy that the mortality from acute appendicitis in the first four years of life is still high and is proportionately higher for the third, second, and first years of life.

General Comment

In the young child the early diagnosis of acute appendicitis assumes great importance because of the rapidly advancing course of the untreated disease. While it is true, as in the older child and adult, that the cardinal clinical manifestations are abdominal pain, vomiting, and localized tenderness, there are important impediments to early diagnosis peculiar to infancy. These include the high incidence of vomiting in extra-abdominal conditions, the resistance to a satisfactory abdominal examination, and the frequent coexistence of respiratory or intestinal infections. The masking of symptoms by previously administered antibiotics may constitute an additional difficulty.

In the infant, abdominal pain may manifest itself only by irritability and restlessness. These symptoms, plus vomiting, occur so frequently in normal infants that a special effort must be made to determine the precise time of their appearance, reappearance, or accentuation in respect to any associated symptoms, such as anorexia, fever, and a change in the sleep pattern. It would seem that there are few diseases in which it is so important to differentiate sharply the present illness from past events.

In order to elicit localized tenderness, it is well to take advantage of a favorable opportunity for a preliminary examination

of the abdomen before the infant's clothes are removed and while the baby is reclining quietly on the mother's lap. Following this, a complete examination must be made and crying may often be avoided by allowing the baby to feed while the abdomen is inspected, palpated, and auscultated. Rectal examination under 2 years of age rarely, if ever, is of help in localizing tenderness, and serves only in the identification of a palpable mass. In the absence of satisfactory cooperation and with sufficient evidence in the history to suspect the presence of an acute surgical abdomen, the use of a sedative in order to facilitate a more thorough reexamination appears justified.

In infants the degree of fever is of little value in the diagnosis of appendicitis. In Norris'[134] series of 1000 children, including cases with perforation, the temperature varied from 97 F to 109 F, and the white blood cell count from 3100 to 60,000. A relative increase of immature polymorphonuclear cells is usually present. In the urine a slight increase in the number of pus cells over the normal three to five per low power field in the uncentrifuged specimen is not unusual. Very little information is obtained from the pulse rate in small infants. In the early months of life, the rate may normally increase to 170 during periods of crying and activity. Abdominal distention and partial ileus with corresponding x-ray findings are almost invariably found when the appendix has perforated, but may occur in gastroenteritis and in pneumonia. Peristalsis is usually normal or diminished in appendicitis and pneumonia and almost always increased in gastroenteritis. The observation that "children ill with pneumonia or other febrile diseases usually sleep for long stretches, but the child with abdominal pain will not sleep and will not let anyone else sleep" is generally true, but rare exceptions occur in which many hours intervene between attacks of pain. Vomiting in acute appendicitis is frequently persistent, but in a substantial minority of cases may occur only once or twice. Constipation may be expected if vomiting is severe. An increased frequency in the number of stools, however, is not unusual and may be mistaken erroneously for an acute enteritis. Diarrhea may occur as the result of stimulation of the contiguous sigmoid colon by an acutely inflamed appendix. Minute amounts of blood are visible in the stool on rare occasions, the pathogenesis of which is not clear. A special subgroup comprises the cases of appendicitis associated with enteritis in which Pseudomonas aeruginosa (Bacillus pyocyaneus) is the predominant organism. Such cases are characterized by necrotizing lesions with ulcerations and occasional perforation, an ordinary type of diarrhea and few or no symptoms characteristic of appendicitis. Leukopenia and agranulocytosis were present in a few of the cases described by Schaffer and Oppenheimer.[155] Statistical evidence that the presence of a coexisting disease renders the diagnosis of acute appendicitis more difficult and increases the incidence of perforation with peritonitis has been presented by Lawrence and Waring.[107] The most frequent error to avoid is failure to entertain the possibility of appendicitis after an original diagnosis of a respiratory infection, gastroenteritis, or acute infectious disease has been made.

In relation to the vast number of appendectomies that are now performed annually in all age groups, the instances of fatalities cannot be considered as being statistically very weighty. However, in the individual case, the fatal outcome of a curable disorder must be regarded as a catastrophe. A high percentage of these catastrophies occurs in infants under 4 years of age (Table 7). An isolated report of a low mortality rate in infants with appendicitis from a single institution does not portray a correct impression of the over-all problem. It is apparent that the status of this disorder is more accurately reflected by an array of figures from many sources. It is thus readily seen from the above statistics that the perforation rate, the mortality rate, and the day of surgery corroborate the introductory

statements that little or no progress has been made in the early diagnosis of appendicitis in infants and that the new therapeutic agents do not always successfully overcome the effects of prolonged delays. Deaver's report [55] is particularly noteworthy in that he found no evidence of a reduction in mortality in his patients by the use of chemotherapeutic or antibiotic agents.

The need to educate continually physicians in every phase of the disorder is obvious. Faulty preoperative preparation of the infant did contribute to the mortality in our series. Educating the parents to seek earlier treatment and to avoid the misuse of cathartics may be helpful, as demonstrated by Bower's reports of the extensive educational program in Pennsylvania. Not infrequently in our series, laxatives and/or repeated enemas were administered on the advice of a physician.

Summary

Thirty-eight cases of acute appendicitis in infants were observed during the 10-year period, 1942 to 1952, at the Los Angeles County Hospital. The incidence of perforation was 81.6% and the mortality was 13.2%. During the same period there were 5354 operations for acute appendicitis in all age groups in the same hospital with a mortality of 1.2%.

The diagnostic difficulties in infants with acute appendicitis are discussed. Analysis of 14 cases with coexisting disease, 5 cases with appendiceal abscess treated "conservatively," and 5 cases with fatal termination are included. An additional case of acute appendicitis with perforation and peritonitis in a 15-day-old infant with survival is reported.

A survey of statistics from the literature confirms the belief that little progress has been made in the early diagnosis of appendicitis in infants.

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Case Reports

Measles in a Newborn Premature Infant

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It has long been appreciated that measles is a rare disease in the newborn infant due to passive transfer of antibodies from the mother to the fetus by way of the placenta.[1,2] It has been a part of pediatric teaching to point out that this immunity is almost absolute for the first five months and relative up to the 8th month.[3] Quite clearly, if the mother has never had measles, either clinical or subclinical, she will have no antibodies to pass on to her offspring.

The first case in the American literature was reported by Smith in 1870.[4] From this time onward a total of 28 cases has been reported in both American and foreign journals.[5-20] No cases have been reported in premature infants so far as this author has been able to discover. This may be due either to intrauterine death or to extrauterine death before the exanthema had a chance to appear. Dyer[5] intimated that the presence of measles in the mother often might be a factor in initiating labor, since out of his 24 cases in pregnant women 45.9% had uterine contractions, resulting in the emptying of the uterus in 37.5%. It is also interesting to note that of the three women who contracted measles in the first trimester and eventually carried their babies to term, there were no abnormalities reported in the baby.

Report of a Case

A boy was born April 2, 1954, at 4:40 a.m. at the U. S. A. F. Hospital, South Ruislip, Middlesex, England.

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Maternal History.—The mother was a 19-year-old woman who had lived all her life in urban areas in England. This was her second pregnancy, and she was presumed to be in her 29th week of pregnancy. The first pregnancy had been complicated by mild toxemia. This pregnancy had been uneventful until one day before the onset of labor, when she developed measles. She had not known she had been exposed and felt quite certain she never had had measles. She appeared only moderately ill. The onset of labor was approximately six hours before delivery. Labor and delivery were considered normal. The serological test for syphilis was negative. The mother's subsequent course was quite uneventful. The rash and all other signs had disappeared in seven days. There was no reason to suspect any illness other than measles.

Physical Examination.—At birth the weight was 1760 gm. (3 lb. 14 oz.); length, 17 in.; temperature, 96 F. The baby appeared in fair condition for a premature infant. The muscle turgor was poor. Respirations were moderately labored and grossly irregular. Scattered rales were heard in both lungs. The skin was thin and transparent. There was very little subcutaneous fat.

Course.—The infant was placed in an incubator with continuous oxygen at 6 liters per minute. Periodic suction was carried out. He was given vitamin K intramuscularly. On the afternoon of the first day of life, he was given 0.2 cc. gammaglobulin. Passage of meconium stools and voiding were noted. The rash of measles appeared on the next day, April 3, 1954, at about 10 a.m. A few Koplick spots were seen in the mouth. There was slight injection of the conjunctivae. Three observers agreed that the rash appeared typical of measles. Initial gavage feeding of 10 cc. of 5% glucose in water was given at 12 noon and was well tolerated. Long periods of apnea and slight cyanosis were observed at about 4 p.m. Shortly afterward the respirations appeared to have ceased. Caffeine was given and artificial respirations were performed. In 10 minutes respirations were reestablished as fairly normal. No further attempts at feeding were made.

The child then seemed in fair condition until about 7 p.m., when he had a brief generalized convulsion. Subsequently the heart rate became slower

and the quality of the beat was poor. The infant was pronounced dead at 9:45 p.m. The rash of measles persisted until moments before death.

An autopsy was refused.

Comment

Since measles undergoes a stage of viremia, it seemed reasonable to try to attenuate the process so far as the infant was concerned by the use of gamma-globulin. In spite of the fact that it apparently had no value in this case, it probably should be used, since no other means for treatment is presently available. It is quite possible that the amount given in this case was inadequate, since Stokes[21] suggests that when using gamma-globulin late in the incubation period, doses 10 to 20 times the usual may offer some protection by way of disease modification or complication prevention.

Summary

A case of congenital measles in a newborn premature infant with fatal outcome is presented. A listing of the American and foreign literature is presented.

Department of Pediatrics, University Hospital.

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Cardiac Tamponade Due to Swallowed Foreign Body

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The frequency with which foreign objects are swallowed by children is well known. We have recently observed a patient in whom a swallowed safety pin perforated through the esophagus into the heart producing cardiac tamponade. Despite prompt diagnosis and therapy, the case terminated fatally because of complications which will be described. This case is reported to call attention of physicians who see children this complication of foreign-body ingestion which we have been unable to find previously reported.

Report of a Case

An 11-month-old white boy was admitted to the pediatric service of the Vanderbilt University Hospital with a complaint of "whooping cough."

The patient's 3-year-old brother was said to have developed pertussis 8 weeks previously. Six weeks prior to admission the patient had developed rhinorrhea, fever, and cough which subsequently became paroxysmal and accompanied by a whoop and vomiting. Ten days prior to admission he had two generalized convulsions and was seen by a physician who made a diagnosis of whooping cough and gave a series of three injections of pertussis hyperimmune serum. Because of failure to improve, he was admitted to the local hospital where he was found to be cyanotic and in severe respiratory distress. Despite oxygen, humidity, and antibiotic therapy, respiratory distress increased and he was referred to Vanderbilt.

There was no history of foreign-body ingestion or aspiration. Family and past histories were nonrevealing except that he had received no immunizations.

Physical examination on admission revealed an acutely ill infant with low-grade fever, tachycardia and tachypnea, inspiratory retraction and an expiratory grunt. The skin was pale but no cyanosis was evident. The lungs were resonant, with harsh breath sounds but no rales or other adventitious sounds. The heart was not enlarged and sounds were of good quality, without murmurs. Blood pressure was 100/60. The liver was felt 3 cm. below the right costal margin, the spleen 2 cm. below the left costal margin. The remainder of the examination was not remarkable.

Initial impressions included (1) pertussis, with a history of encephalopathy; (2) anemia, and (3) ? bronchopneumonia.

Admission laboratory findings included the following: WBC 36,500/cu. mm., with 10% juveniles, 77% neutrophiles, and 13% lymphocytes. Hgb 7.5 gm/100 cc. with RBC indices indicative of a microcytic, hypochromic anemia. Urinalysis normal. Histoplasmin and tuberculin skin tests negative. N. P. N. 24 mg/100 cc.; CO_2 combining power 22.5 mEq/L.; Cl 94.8 mEq/L.; Na 120 mEq/L.; K 5.3 mEq/L.; TSP 4.6 gm/100 cc. and A/G 2.7/1.9.

Roentgenograms of the chest revealed an open safety pin in the esophagus with the point directly upward in close proximity to and possibly within the cardiac silhouette (Figure). There was a diffuse scattered infiltration throughout both lung fields and widening and mottling of the mediastinal shadow suggestive of a mediastinitis.

Esophagoscopy * was performed, the pin pushed into the stomach, rotated, and on withdrawal found to be rusted. The operator was unable to determine whether or not perforation of the esophagus had occurred. After intradermal testing, tetanus antitoxin was administered.

On the second hospital day Pseudomonas aeruginosa was recovered from cultures of the throat and nasopharynx and a coliform organism from the blood. On the basis of in vitro sensitivities, chloramphenicol 125 mg. every 6 hours and streptomycin 250 mg. every 12 hours were given intramuscularly; the former was continued throughout hospitalization. The infant was maintained in oxygen and moisture and on intravenous fluids, including whole blood for correction of the anemia. Because of the history of convulsions, a lumbar puncture was performed; this was productive of normal spinal fluid with free dynamics, normal chemistries, and sterile cultures.

No significant change occurred in the infant's condition until the fourth hospital day, when he

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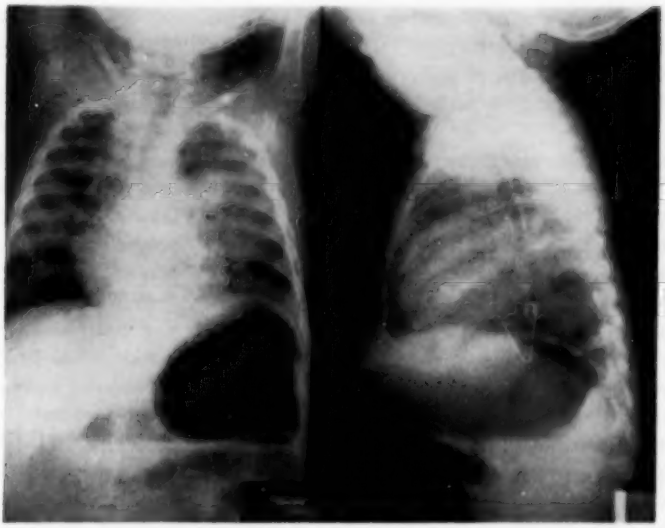
* Performed by Dr. Guy Maness, Department of Otolaryngology.



developed increasing periorbital and pedal edema and heart sounds became very distant. Venous pressure was found to be 340 mm. of saline and ECG revealed low voltage and abnormal T-waves. Chest roentgenogram revealed an increase in heart size and an air-fluid level within the pericardial space.

The infant was taken to the operating room where, under local lidocaine (Xylocaine) hydrochloride anesthesia, pericardiostomy † was performed with the release of approximately 100-150 cc. serosanguinous fluid under considerable pressure. Culture of this fluid later yielded coliform organisms, Pseudomonas aeruginosa, and a yeast. Immediately upon release of the pericardial fluid, the infant exhibited marked reduction in respiratory distress and began to struggle vigorously on the table.

Postoperatively, the infant was maintained for a six-day period on intravenous fluids. Multiple small transfusions of whole blood and salt-poor serum albumin were given without elevation of the albumin fraction of the total proteins. He remained febrile during this period, temperature ranging from 101 to 103 F rectally. On the fourth postoperative day peripheral edema began to increase. Venous pressure at this time was 130 mm. and ECG showed only ST changes. Drainage from the pericardium was small in amount, serous in character, and sterile on culture. Repeat blood cultures after seven days of antibiotic therapy were sterile.

On the sixth postoperative day, because of the increasing edema and development of basilar rales, digitalization was begun with digitoxin. A small volume of glucose water containing methylene blue was given by mouth without appearance of dye on the pericardiostomy dressing after three hours. A tube was then passed into the upper esophagus and chloriodized oil (Iodochloral) injected under fluoroscopy; this passed freely into the stomach without extravasation from the esophagus. Accordingly, tube feedings were initiated, first providing glucose water, then skim milk fortified with additional protein.

On the tenth postoperative day examination of the chest revealed dullness to percussion over the right anterior and lateral chest and greatly diminished breath sounds. The liver was felt 6 cm. below the right costal margin. Roentgenograms showed a bilateral pleural effusion, more extensive on the right. He died on the following day.

Postmortem Findings ‡

The autopsy examination was begun approximately three hours after death. Only the pertinent findings will be presented.

Gross Examination

The right pleural cavity contained approximately 10 cc. of straw-colored fluid, and the right lung was expanded and free of adhesions. The left lung, however, was completely covered with a thick fibrous and

† Performed by Drs. Sam Stephenson and H. William Scott, Department of Surgery.

‡ Performed by Drs. D. L. Beaver and J. L. Shapiro, Department of Pathology.

fibrinous exudate and was adherent to the chest wall and surrounding structures. The mediastinal tissues, especially posteriorly, appeared edematous and inflamed, with crepitation.

The pericardium was markedly thickened and was adherent to the epicardial surface of the heart, which was covered by a thick fibrous coat. Two or three centimeters above the cardia on the anterior aspect of the esophagus was a small perforation, 1 mm. in diameter, through which a probe entered the pericardial cavity posteriorly beneath the inferior vena cava in the angle formed by it and its junction with the right auricle. The endocardium was smooth and shiny except on the posterior aspect of the right ventricular wall where a mural thrombus or vegetation measuring 0.5×0.5 cm. was attached by a thin pedicle to the endocardium above the posterior tricuspid leaflet. On cut section its center was seen to consist of purulent material. The myocardium itself was somewhat opaque and flabby. The pulmonary, aortic, and mitral valves were not remarkable. There was a patent foramen ovale 1 cm. in diameter covered by a valvulae foraminis ovalis.

The lower lobe of the right lung was studded by hard, raised, bluish nodular areas, subpleural in location and pyramidal in shape. These areas were markedly hemorrhagic and were typical of infarcts. Below the apex of one of these areas a small embolus was found in a pulmonary vessel. Adjacent to these areas and in the remaining pulmonary tissue of the right lower lobe, there were multiple small focal areas of suppuration. Similar smaller areas were observed in the left lung.

Microscopic Examination

The esophageal mucosa was intact, except at one point, where it was apparently avulsed. The interposed connective tissue contained only a slight infiltrate of chronic inflammatory cells; the fistulous tract, however, was surrounded by granulation tissue. The regional lymph nodes were infiltrated to some extent with large mononuclear phagocytes. The pericardium was fibrous, cellular, and considerably thickened. There was widespread evidence of pericarditis, and attached to the endocardium by a narrow pedicle was a vegetation consisting of an amorphous network of interlacing fibrin strands with interwoven cellular debris and degenerating polymorphonuclear leucocytes. No bacterial colonies or fungi were seen.

The lungs revealed areas of suppuration, some undergoing central liquefaction, surrounded by a zone of eosinophilic, amorphous, necrotic material containing cellular debris. One area presented more of the typical picture of bland infarction, being hemorrhagic and containing a diffuse infiltrate of acute inflammatory cells. Several of the pulmonary vessels contained thrombi, some just beginning to undergo organization, others completely recanalized. There was no histologic evidence in the tracheobronchial tree of pertussis.

In summary, the autopsy revealed an esophagopericardial fistula with an associated mediastinitis and an organizing adhesive pericarditis. There was an endocardial vegetation in the right atrium and multiple infarctions of the lungs secondary to septic emboli. Microscopically, the fistulous tract was composed predominantly of granulation tissue and was well on its way toward complete organization, which would set the duration of the perforation in weeks. Pseudomonas aeruginosa was cultured from the lungs and Candida albicans was grown from the endocardial vegetation; the latter was thought to be a contaminant, since the yeast could not be found on tissue sections.

Comment

In reconstructing the train of events in this case it would seem that the swallowed safety pin, after lodging in the esophagus, had perforated through the esophagus and pericardium into the right atrium. Subsequently a fistulous tract between the esophagus and the pericardium had formed. The condition of the removed pin, the micro-

scopic appearance of the esophagopericardial fistula, the organizing mediastinitis and pericarditis, and the presence of endocardial vegetations indicate that the process was of several weeks duration and was not related to endoscopic removal. It is likely that the leakage of esophageal contents was hastened when the lumen of the fistulous tract was enlarged by the removal of the pin. In all probability the increased intraesophageal pressure occasioned by the paroxysms of coughing forced foreign material through the tract into the pericardium with gradual accumulation of pericardial fluid and development of cardiac tamponade. The latter was successfully relieved, but, unfortunately, endocardial vegetations had developed followed by pulmonary emboli which were the immediate cause of death. Because of the long interval since the onset of symptoms suggestive of pertussis, the absence of histologic evidence in the tracheobronchial tree of pertussis does not necessarily eliminate this disease. The clinical manifestations and the history of a similar illness in a sibling was quite suggestive of pertussis. However, it is entirely possible that the paroxysmal cough was due solely to mediastal irritation by the pin.

The upper portion of the esophagus just below the cricopharyngeal constriction is the most frequent site of impaction of swallowed foreign bodies. Impaction in this area produces distinct sysmptoms, but when the foreign body is small and lodges in the lower end of the esophagus, the signs may be quite obscure.[1,2] The many pathologic changes produced by foreign bodies in the esophagus are associated with obstruction, stenosis, ulceration, erosion, and perforation of the esophagus.[3] As a rule foreign bodies are adjusted by the yielding movements of the esophgus to a position least likely to cause trauma. Safety pins, which as foreign bodies are most commonly found in the age period 7 months to 2 years, usually turn over and descend with the spring end leading.[2] Sharp foreign bodies may perforate the esophagus soon after being swallowed but more commonly complications secondary to perforation are the result of foreign bodies remaining in the esophagus for long periods or to ineffectual attempts at their removal.[1]

Aortic perforation by a swallowed foreign body has been described.[4,5] Watkyn-Thomas [1] refers to a surgical exhibit in the Herbert Tilley Museum in London, which reveals perforation of the aorta by a coin extruded through the esophageal wall. Holinger and Johnson [3] cite the case of an infant who developed a fatal carotid aneurysm six months after removal of a safety pin from the upper esophagus. In 1860 there was reported the case of a woman who was found at autopsy to have perforation of the heart with fatal laceration of the coronary vessels secondary to a swallowed fish bone which had perforated the esophagus.[6] In 1873 Callender, in reviewing cases of cardiac perforation by foreign bodies entering through the thoracic wall, alluded to the case of an adult in whom a fish bone penetrated through the stomach into the heart. [7]

A fatal case of subacute endocarditis due to Monilia apparently originating from a toothpick located within the heart of a 58-year-old woman has been recently observed at this hospital. At autopsy no evidence of esophageal or epicardial perforation was found, and it was felt that the foreign body had probably perforated the intestinal tract below the stomach and reached the heart by intravascular pathways.[8]

A search of the literature, however, reveals no reported cases of cardiac tamponade in infancy or childhood secondary to a foreign body in the esophagus. None of the standard textbooks of otolaryngology [1,2,9-11] include such a case and no instance of such a complication is mentioned in the extensive treatise of Jackson and Jackson devoted only to diseases produced by foreign bodies in the food and air passages.[5] Furthermore several experienced endoscopists [4,12-14] stated that they had not observed such a complication.

In view of the frequency of swallowed sharp objects in infancy and childhood, it would seem that complications of this nature would be a relatively common occurence. Such apparently is not the case. However, in the presence of clinical manifestations of cardiac tamponade, an extremely rare occurrence in infancy and childhood, the possibility of cardiac perforation by a swallowed foreign body should be considered.

Summary

A case of cardiac tamponade caused by perforation of a swallowed safety pin through the esophagus into the heart in an infant is reported. Despite antemortem diagnosis and relief of the cardiac tamponade, the case terminated fatally due to pulmonary emboli originating from endocardial vegetations. To our knowledge no similar case of cardiac tamponade of this genesis has been reported previously.

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Archives of Disease in Childhood, London

31:1-68 (Feb.) 1956

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Attacks of Unconsciousness in Association with Fused Cervical Vertebrae. R. S. Illingworth.—p. 8.
Nephritis in Childhood. Norman S. Clark.—p. 12.
Fibrocystic Disease of the Pancreas in the Newborn. Albert E. Claireaux.—p. 22.
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A Chemical Study of Mucin in Fibrocystic Disease of the Pancreas. Charlotte Anderson and Mavis Freeman.—p. 31.
* The Hyaline Membrane Syndrome in Premature Infants. William Blystad.—p. 33.
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The Pattern of the Electrolyte Excretion in the Urine of Babies Born to Diabetic Mothers. Thomas Stapleton.—p. 42.
* Thirty-Three Cases of Subdural Effusion in Infancy. E. Herzberger, Y. Rotem, and J. Braham.—p. 44.
Bilateral Wilms' Nephroblastoma. Gerald B. Doyle.—p. 51.
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Rupture of the Stomach in the Newborn Due to Congenital Defects in the Gastric Musculature. P. C. MacGillivray, A. M. Stewart, and A. FacFarlane.—p. 56.
Familial Pitressin-Resistant Diabetes Insipidus with Mental Defect. B. H. Kirman, J. A. Black, R. H. Wilkinson, and P. R. Evans.—p. 59.

31:69-152 (April) 1956

Clinical and Pathological Details of Two Cases of Phaeochromocytoma in Childhood. M. J. Robinson and Alan Williams.—p. 69.
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The Recognition of Primary Tuberculous Infection of the Mouth. J. Boyes, J. D. T. Jones, and F. J. W. Miller.—p. 81.
Whooping Cough Encephalitis. A. L. Woolf and H. Caplin.—p. 87.
Hydrops Foetalis Successfully Treated by Exchange Transfusion. Josephine Cook.—p. 92.
Laryngeal Stenosis with Tracheostomy Treated by Hemi-Laryngectomy and Reconstruction of the Laryngeal Orifice. H. S. Sharp.—p. 94.
Klebsiella Pneumoniae (Friedlander's Bacillus) Infections in Infancy. Bela Steiner and Gyula Putnoky.—p. 96.
Acute Glomerulonephritis in Infancy. T. N. Fison.—p. 101.
Hydronephrosis in Infancy. A. R. Bearn.—p. 110.
A Histochemical Study of Pulmonary Hyaline Membrane. F. Duran-Jorda, A. Holzel, and W. H. Patterson.—p. 113.
Radiological Findings in the Lungs of Premature Infants. John Fawcitt.—p. 119.
Single Polyp of the Large Intestine in Childhood. J. R. Hughes, R. T. Jenkins, and D. E. Sturdy.—p. 124.
* Blood Pressure in the Newborn Estimated by the Flush Method. John O. Forfar and Maurice A. Kibel.—p. 126.
Coexistent Aplastic Anaemia and Coarctation of the Aorta. J. P. Anderson.—p. 131.
Subcutaneous Emphysema Complicating Asthma. J. R. K. Henry.—p. 133.
Clinical Aspects of Congenital Tuberculosis. F. P. Hudson.—p. 136.
Studies in a Case of 'Renal Rickets.' Kenneth Sinclair.—p. 140.
Exomphalos. A. A. Cunningham.—p. 144.
Pediatric Societies in the British Isles.—p. 152.

The Hyaline Membrane Syndrome in Premature Infants.—The clinical data and the necropsy findings of 47 premature infants who died in the course of the early neonatal period were examined. Early neonatal dyspnea was observed in 25 patients. In all cases there was extensive atelectasis. In 15 of these the necropsy revealed hyaline membrane in the lungs. The other patients with this clinical picture also showed marked pulmonary changes. The clinical picture reflected a pulmonary pathology of varying character in which marked atelectasis of unknown origin was a constant finding.

In 22 patients respiration was depressed centrally. In these intracranial hemorrhage was found somewhat oftener but was not a precondition to the establishment of this clinical picture. In this group considerable pathological changes were also frequently found in the lungs. In

seven cases the necropsy revealed hyaline membrane. It is probable, in spite of the lacking dyspnea, that pulmonary changes were the main cause of the asphyxia in some of the patients in the second group.

Thirty-Three Cases of Subdural Effusion in Infancy.—A series of 33 cases of subdural effusion in infancy is presented. In only 4 was there a reasonable certainty of a traumatic etiology; 15 followed purulent meningitis, and in 12 the effusion appeared in the course of a general illness with gastroenteritis, malnutrition, and bronchopneumonia.

In seven of the cases (five postmeningitic and two "gastroenteritic") the effusions responded to evacuation by repeated taps, some 8-15 ml. of fluid being removed on each occasion.

Failure of the effusion to respond to this simple measure led to the performance of burr holes in 22 patients. Fluid was evacuated and the brain and its coverings inspected. Membrane was seen in half of the infants submitted to this procedure. In two cases the membrane (unilateral) was thick, greenish, and adherent to the arachnoid and was removed at subsequent craniotomy (the post-Hemophilus meningitis and the hydrocephalus cases, respectively). In the remaining nine cases the membrane was thin, whitish, and applied only to the inner surface of the dura but not adherent to the arachnoid.

Repeated taps, from two to four in number, sufficed to bring about apparent cure in five meningitis cases and in two enteritis- malnutrition cases. All 6 of the 22 submitted to burr holes in whom no brain damage was seen did very well.

In a group on 11 cases of brain damage without membrane, 7 improved but were not considered to do as well as those without brain damage.

In a group of eight cases with brain damage and well-marked membrane, three died and three improved and in two the results were good. Craniotomy was performed in only two patients in the entire series.

The authors were satisfied at the time these children were treated that clinical recovery was either rapid and complete or compatible with what could be expected in the light of existing brain damage.

A Study of Serum Bilirubin Levels in Relation to Kernikterus and Prematurity.—The staining of the basal ganglia in various conditions not associated with isoimmunization has aroused much interest in recent years. Kernicterus has been described associated with acholuric family jaundice, idiopathic familial hyperbilirubinemia, and sometimes with prematurity only. The clinical picture of the premature infant who becomes jaundiced on the third or fourth day of life and by the sixth day exhibits profound jaundice, disinclination to feed, head retraction, changes in muscle tone and cyanosis, and in most cases dies on the sixth or seventh day have been described. Whatever else has occurred, the pigment in the brains of these infants at necropsy is bilirubin. Whether the bilirubin is toxic or not, it does appear to be the common factor of all these theories.

The present study shows the curves of serum bilirubin levels on 93 babies of all weight groups and indicates that babies under 2000 gm. (4 lb. 6 oz.) have levels still rising on the sixth day, babies of 2000 to 2500 gm. leveling out, and levels of babies over 2500 gm. are falling by the sixth day.

Premature babies developing kernicterus have generally higher serum levels of bilirubin and the majority have levels of over 18 mg. per 100 cc. at the onset of signs. Kernicterus is very likely to occur where serum levels of bilirubin rise above 18 mg. per 100 cc.

There appears to be no critical level of bilirubin in the C. S. F. at which staining of basal nuclei takes place and there is no correlation between the bilirubin levels in the serum and that in the C. S. F.

It is suggested that all jaundiced premature babies should have serial bilirubin estimations, the frequency of those estimations depending on the level of bilirubin and the rate of rise of that level.

It is suggested further that replacement transfusion may be effective in the prevention of kernicterus in babies whose serum bilirubin levels are above 18 mg. per 100 cc. or whose rate of rise is rapid.

Blood Pressure in the Newborn Estimated by the Flush Method.—Five hundred thirteen blood pressure estimations have been carried out on 143 newborn infants (aged 0-11 days) using the flush technique.

The technique is described.

An assessment is made of the accuracy of the method, and it is concluded that, although it is less accurate than the auscultatory method in the older child or adult, it is a useful clinical procedure.

The pressures given by the method described represent approximately the mean systolic-diastolic blood pressure.

During the first 11 days of life blood pressure increases significantly with age and shows a positive correlation with birth weight.

The normal range of blood pressure in the first 11 days of life averages 59.5 at birth to 88 at age 10 days in the arm, and 65 at birth to 99 at age 10 days in the leg.

In 90% of readings the blood pressure in the leg is higher than that in the arm.

The probabilities of occurrence of various degrees of reversed arm/leg pressures which may be encountered in the normal newborn infant are given.

Crying was found to increase the blood pressure by an average of 7.5%.

No sex difference was found.

Blood, New York

11:403-500 (May) 1956

* Anti-A Agglutinins in Pooled Plasma as a Cause of Hemolytic Anemia. Julius Rutzky, Flossie Cohen, and Wolf W. Zuelzer.—p. 403.

Sickle-Cell Anemia in South Turkey: A Study of 15 Cases in 12 White Families. Muzaffer Aksoy.—p. 460.

Immunization of Rabbits Against Human Anti-Hemophilic Factor (AHF). Marvin D. Richards and Theodore H. Spaet.—p. 473.

Anti-A Agglutinins in Pooled Plasma As a Cause of Hemolytic Anemia.—Administration of pooled plasma to recipients of all ABO groups has been generally regarded as safe because of the assumed dilution and neutralization of the anti-A and anti-B isoantibodies in the pool. However, this study demonstrates a real risk of hemolytic reaction involved in the administration of large quantities of pooled plasma to recipients of blood group A_1 and presumably also B and A_1B.

Acute hemolytic episodes were observed in A_1 recipients, and these were demonstrated to be related to the anti-A isoantibodies in pooled plasma.

During the hemolytic episodes in five group-A patients following prolonged administration of large amounts of pooled plasma, spherocytosis, increased in osmotic fragility, rising bilirubin levels, and sometimes clinical jaundice and splenomegaly were observed. The Coombs' test demonstrated antibody attached to recipients' cells and in some patients free antibody of anti-A specificity was found in the recipients' plasma.

Random testing of commercial pooled plasma revealed high anti-A titers, indicating the relative ineffectiveness of dilution in the pool or neutralization by anti-A substance. The administration of relatively large amounts of pooled plasma of low titer (1:16) was not followed by a hemolytic reaction. However, administration of originally high titered plasmas neutralized in vivo to a saline titer of 1:16 resulted in blood destruction, indicating that under conditions of prolonged massive administration, specific soluble substance is inadequate.

These studies emphasize the potential hazard of prolonged administration of untitered pooled plasma to recipients of groups A and probably B.

Canadian Medical Association Journal, Toronto

74:501-600 (April 1) 1956

* The Future of the Deaf Child. R. W. Fanjoy.—p. 533.

Potter's Facies Associated with Polycystic Kidney, with Laurence-Biedl-Moon Syndrome in Siblings. Agnes E. Bimbi-Kovacs and A. F. Hardyment.—p. 549.

74:863-956 (June 1) 1956

* Congenital Malformation of the Anus. J. A. Palmer.—p. 882.

Phenylketonuria: A Survey of Cases at the Manitoba School. R. Gibson.—p. 897.

74:957-1028 (June 15) 1956

* Experiences with Oral Sulfonamide (BZ-55) in the Management of Juvenile Diabetes. A. L. Chute and H. W. Bain.—p. 994.

75:1-92 (July 1) 1956

Research on the Development of a Poliomyelitis Vaccine: Toronto, 1950-1953. A. J. Rhodes.—p. 48.
* The Clinical Effects of Chlorpromazine in Cerebral Palsy. F. J. Day and J. L. Gulley.—p. 34.

The Future of the Deaf Child.—The author, the father of a deaf child, discusses methods of diagnosis of deafness in a young child, as well as the answers to many questions posed by parents such as "Will my child ever talk?" "Will my child ever hear?" "If we have another baby will he also be deaf?" etc. He gives illustrative answers to many questions, going into considerable detail.

The future of a deaf child is dependent upon the combined efforts of the home, school, general public, and physician, and it is suggested that the four cardinal virtues in the training of a deaf child are 1. Faith (by parents), 2. Hope (by school for parent cooperation), 3. Understanding (by the public), and 4. Guidance (by the physician).

Congenital Malformation of the Anus.—The author discusses diagnosis, treatment, and results of treatment in 100 cases of anal malformation seen at the Hospital for Sick Children, Toronto. The cases were classified after Ladd and Gross into four groups. Approximately one-half the cases were associated with fistulae. Also frequently associated with the lesion were single or multiple congenital anomalies. Treatment of simple stenosis (Eight cases) by repeated dilatation was quite satisfactory. Treatment of membranous anal imperforation (Nine cases) by cruciate incision and dilatation was very successful. Treatment of other types was less successful and depended upon several factors.

Experiences with Oral Sulfonamide (BZ-55) in the Management of Juvenile Diabetes.—Five children with diabetes mellitus were treated with BZ-55 (carbutamide). Three children had recently discovered diabetes and were given BZ-55 instead of insulin for three to five days. No lowering of the blood sugar was demonstrated. Two children with long-standing diabetes were studied. One failed to show hypoglycemic effect over a period of three weeks. The second showed a definite BZ-55 effect as regards maintenance of a relatively normal fasting blood sugar, but no effect on postprandial blood sugar levels.

N. B. This issue of the Canadian Medical Association Journal is concerned entirely with the experimental and clinical effects of BZ-55.

The Clinical Effects of Chlorpromazine in Cerebral Palsy.—Twenty-two patients (children) with athetoid or spastic cerebral palsy were treated with chlorpromazine at the Edmonton Cerebral Palsy Clinic. Motor age tests were used to judge improvement. About 36% of cases tested had definite effect, sufficient to make their treatment more beneficial. The authors recommend that chlorpromazine be at least considered in all cases of cerebral palsy while they are under treatment in a clinic. They do not indicate the amount of chlorpromazine used.

Journal of the American Medical Association, Chicago

161:569-670 (June 16) 1956

* Neuropsychiatric Sequelae of Prematurity. Hilda Knoblock, Rowland Rider, Paul Harper, and Benjamin Pasamanick.—p. 581.
Palatine Petechiae, an Early Sign in Infectious Mononucleosis. C. B. Shiver Jr., Perry Berg, and E. P. Frenkel.—p. 592.
Venostomy, an Improved "Cut-Down" Procedure in Infants and Children. J. V. Miles Jr. and L. E. Harris.—p. 619.

161:671-774 (June 23) 1956

Treatment of Enterobiasis with One Oral Dose of Promethazine Hydrochloride. J. L. Avery.—p. 681.
* Severe Toxic Effects from Aminophylline and Theophylline Suppositories in Children. A. C. Nolke.—p. 693.
Mechanical Respirator for Newborn Infants and Other Patients. A. R. Bauer.—p. 723.
Current Trends in the Feeding of Infants and Children. C. A. Smith.—p. 728.

161:775-934 (June 30) 1956

Immunogenicity in Children of Ultraviolet-Treated Poliomyelitis Vaccine. A. M. Wolf, H. J. Shaughnessy, R. E. Church, Albert Milzer, Martha Janota, Franz Oppenheimer, R. A. Morrissey, Henry Naftulin, J. W. Chapman, and S. O. Levinson.—p. 775.

* Prognostic Studies in Children with Cerebral Palsy. Eric Denhoff, R. H. Holden, and M. L. Silver.—p. 781.

Prevention of Congenital Syphilis by Treatment of Syphilis in Pregnancy. N. A. Nelson, and V. R. Struve.—p. 869.

161:935-1034 (July 7) 1956

The Team Approach to Hearing and Speech Disorders. Robert Henner, F. J. Pollock, P. A. Campanelli, Doris Phillips, and Margaret Judiesch.—p. 957.

Kartagener's Syndrome in a Newborn Infant. S. J. Nichamin.—p. 966.

161:1035-1118 (July 14) 1956

* Causes and Prevention of Developmental Defects. Theodore H. Ingalls.—p. 1047.

161:1119-1212 (July 21) 1956

Blood Replacement in Thoracic Surgery for Children. R. M. Smith.—p. 1124.

161:1213-1344 (July 28) 1956

Physical and Physiological Clues for Diagnosing Eczema. W. C. Lobitz and R. L. Dobson.—p. 1226.

Habilitation of the Child with Spina Bifida and Myelomeningocele. S. S. Bluestone and G. G. Deaver.—p. 1248.

161:1345-1432 (Aug. 4) 1956

Acute, Subacute, and Chronic Subdural Hematoma. F. A. Echlin, S. V. R. Sordillo, and T. Q. Garvey.—p. 1345.

* Current Preventive Problems of Child Health. Lesli Corsa.—p. 1361.

Determination of Radioiodine Uptake in Thyroids by Two Methods. Egisto DeAmicis and E. W. Williamson.—p. 1377.

161:1521-1604 (Aug. 18) 1956

* Postmaturity and the Placental Dysfunction Syndrome. R. H. Kunstadter and S. E. Schnitz.—p. 1551.

* Etiology and Mechanism of Harrison's Grooves. H. A. Brodkin.—p. 1555.

Thrombocytopenic Purpura Resulting from Sulfisoxazole (Gantrisin) Therapy. T. W. Green and J. Q. Early.—p. 1563.

Elkosin in the Management of Urinary Tract Infections. Morton Bogash, Helen Ellis, and J. J. Murphy.—p. 1564.

Neuropsychiatric Sequelae of Prematurity.—The authors tested the mental and physical status of 992 infants using the Gesell developmental examination as a basis for the former. Of the 992 infants there were 500 single born-premature infants and 492 infants born at term. The examinations were made at 40 weeks for the full-term infants and at the corresponding corrected age for the premature infants. A comparison was made between the two groups, the groups having first been matched as to race, socioeconomic status, and other significant factors.

The analysis of the findings showed that the incidence of neurological and intellectual defects increased as the birth weight of the infant decreases. The expected over-all incidence of serious neurological abnormality (possible cerebral palsy plus overt neurological defect) in premature infants was 8.2%, significantly higher than the rate of 1.6% in the controls. For mental deficiency the expected rate is 2.6%, not significantly higher than the rate of 1.6% in the full-term infants. Of the infants with a birth weight less than 1501 gm., 50.9% had a neurological or intellectual defect; some of these also had a major visual handicap. The adjusted percentage of premature infants who show some departure from normal development is 25.7%, compared with 12.8% of the full-term controls.

Severe Toxic Effects from Aminophylline and Theophylline Suppositories.—The findings of 13 children with severe toxic reaction to theophylline given by rectal administration are presented. The ages ranged from 5 months to 6 years. There were four deaths in this series of patients. The symptoms were frequent vomiting, unusual thirst, and maniacal agita-

tion. In the severest cases the vomitus became brown and syrup-like, and delirium, convulsions, and shock appeared.

Autopsy findings were inconspicuous except for the finding of pulmonary inflammation in all four classes and of ucerative esophagitis with perforation in two. The author states that the use of aminophylline by rectal administration is to be deprecated and calls for a reconsideration of the dosages now in use.

Prognostic Studies in Children with Cerebral Palsy.—This study attempts to evaluate the validity of pneumoencephalography and psychological examination in predicting the future adjustment of 50 cerebral palsied children.

There was an over-all agreement of 81% between the initial psychological predictions and the actual clinical progress and 72% agreement between the initial pneumoencephalographic predictions and the actual clinical progress. On the basis of the results it would appear that early psychological test predictions are valid indicators of future adjustment. Pneumoencephalograms can often clarify the prognosis. Electroencephalography was not a reliable prognostic tool; however, it did prove of value in the diagnosis of seizures in the cases presented. The authors emphasize that family attitudes must not be overlooked in prognostic assessment. A related study by two of the authors emphasized that good environment can counteract, in some measure, poor physical and intellectual status.

Causes and Prevention of Developmental Defects.—Extensive researches carried on at the Harvard School of Public Health during the past decade indicate that most congenital anomalies originate as fetal manifestations of critical stress in pregnancy. Examples are cited of Mongoloid infants being born of mothers who had some type of stress during the second month of pregnancy. The scientific method of studying this concept is described and consists basically of a low-pressure chamber in which pregnant mice are kept for varying periods of time at various periods during pregnancy. The authors found that the type of malformation depended upon the stage of development that had been reached when hypoxic stress was administered.

The statement is made that the evidence is overwhelming that many, if not most, anomalous children have survived a temporary intrauterine stress.

Current Preventive Problems of Child Health.—The author discusses what is considered to be the major preventible problems of child health at the present time. In considering the problem of premature birth he stresses that greater emphasis should be placed on the prevention of premature delivery itself. He suggests that this be done by the following methods: (1) the provision of good prenatal care to all pregnant women; (2) the development of maternal and perinatal mortality committees to study the preventability of these deaths; (3) further research into the cause of prematurity. He suggests that the definition of prematurity be sharpened.

The topic of accident prevention is directed toward the private physician and the point is stressed that the private physician should discuss with parents the dangers of poisonings, burns, etc., and how such accidents can be prevented.

The preventive aspect of infectious, chronic, and mental illnesses are also mentioned.

Postmaturity and the Placental Dysfunction Syndrome.—Maternal and neonatal charts, numbering 2877, were reviewed to determine the incidence of postmature births. Infants with gestational ages of 294 days and over were classified as postmature. The incidence of postmaturity in this series was 8.59% in infants 294 days and over and 4.59% in infants 300 days or more. The authors appraised the race, sex, weight, length, physical appearance of the baby as described by the examining physician and nurse, morbidity, mortality, and postmortem findings. Two hundred fifty-two infants born during the same period were used as controls.

Comparison of birth weights and heights revealed that postmaturity does not signify a large baby. Perinatal mortality did not appear to be significantly higher in postmature babies than in full-term infants. There was, however, a definite placental dysfunction syndrome that occurs oftener in postmature infants than in those of average gestational age. Because the syndrome is not confined exclusively to postmature infants, the authors suggest that the term postmaturity syndrome be discarded.

Etiology and Mechanism of Harrison's Grooves.—The etiology and mechanism of Harrison's grooves have remained controversial and unsettled since first described some 120

years ago. They are ascribed either to rickets or to increased negative pressure due to chronic respiratory difficulty in infancy. In the author's studies of the action of the diaphragm and its relation to the development of the normal thorax as well as to the development of the other anterior-chest-wall deformities (funnel chest and pigeon breast) evidence is given to support the theory that all three deformities are produced by abnormal contractions of the diaphragm during infancy. Unbalanced diaphragmatic contractions will produce an inspiratory retraction of some portion of the chondrosternal area if the anterior portion of the diaphragm is congenitally weak or deficient or if abnormally strong diaphragmatic contractions are induced by chronic dyspneic conditions when the anterior chest wall is still soft and yielding.

Journal of Clinical Investigation, New York

35:453-577, 1956

The Production and Identification of Antibodies to Insulin and Their Use in Assaying Insulin. Edward R. Arquilla and Abram B. Stavitsky.—p. 458.

Evidence for the Insulin-Directed Specificity of Rabbit Anti-Insulin Serum. Edward R. Arquilla and Abram B. Stavitsky.—p. 467.

* Placental Passage of 17-Hydroxycorticosteroids: Comparison of the Levels in Maternal and Fetal Plasma and Effect of ACTH and Hydrocortisone Administration. Claude J. Migeon, Harry Prystowsky, Melvin M. Grumbach, and Margaret C. Bryson.—p. 488.

The Effect of Glucagon on Carbohydrate Metabolism in Normal Human Beings. Philip K. Bondy and Leo R. Cardillo.—p. 494.

Placental Passage of 17-Hydroxycorticosteroids: Comparison of the Levels in Maternal and Fetal Plasma and Effect of ACTH and Hydrocortisone Administration.—The role of placental transmission of free 17-hydroxycorticosteroids has been unclear. A progressive rise in plasma levels has been observed during pregnancy by many investigators, and an increase in urinary glucocorticoids. Adult concentrations have been found in the umbilical vein after vaginal delivery, but much lower levels after caesarian section. The site of production of these has not been elucidated. The rise in plasma levels of pregnant Addisonian patients has suggested an extra-adrenal source, possibly the placenta. The prompt decrease in infant levels after delivery and the low values at birth of those born by section may indicate a lack of fetal production. The constant ratio of maternal and umbilical vein levels in those born by vaginal delivery has suggested that fetal values only reflect maternal levels.

To elucidate the problem, measurements were made in 9 cases of vaginal delivery, and in 5 cases of indicated section; 19 cases of elective repeat section were also studied, including 7 after a prepartum infusion of ACTH, and 5 after an infusion of hydrocortisone. Blood samples were taken during labor, at delivery, and on the third postpartum day. Comparison of results show higher predelivery levels by some three times in those undergoing labor. Despite the authors' statement to the contrary, there is little difference in all groups between the "predelivery" and "at-delivery" ratios, indicating that parturition itself vs. section is of less importance than labor in 17-OH-CS production. Cord values were always less than maternal values, irrespective of the method of delivery. Levels in those born by elective section (without labor) were considerably lower than in the other two groups.

The response to ACTH infusion was similar to that found in the nonpregnant. Cord levels were one-third to one-half maternal levels and all were significantly higher than those not stimulated by ACTH.

The striking increase in 17-OH-CS levels after compound F was directly proportionate to the amount administered. Although markedly elevated, cord values were again only one-third of maternal levels. Comparison of cord levels, however, with the control group of elective sections demonstrated a passage of compound F through the placenta, cord values being 10 to 25 times greater in the infused group. It appears also that mere diffusion is not the determining factor but a certain threshold level in the maternal circulation.

It is not known whether increased maternal levels indicated increased production, since all factors regarding degradation and excretion are not known. It does appear from pregnant Addisonian patients, however, that there are extra-adrenal sources, possibly the maternal side of the placenta. In addition, the fetal adrenals produce little or no 17-OH-CS at this time, normal adult levels not being reached until after the first week of life. In contrast, fetal levels of 17-ketosteroids are higher than maternal levels. These tend to fall gradually in the first few weeks after birth and do not rise again until the onset of puberty.

Medical Journal of Australia, Sydney

1:121-160 (Jan. 28) 1956

The Control of Infectious Disease, with Special Reference to the Hospital. H. McLorinan.—p. 121.
Control of Infectious Diseases. D. W. Johnson.—p. 123.
Control of Infectious Disease in a Rural Community. Clifford Jungfer.—p. 129.
The Induction and Control of Hypothermia. M. H. Cass, A. F. A. Harper, and R. G. Wylie.—p. 134.

1:205-264 (Feb. 11) 1956

The Pathogenesis of Poliomyelitis. Frank Fenner.—p. 205.
Introduction to a Symposium on Rheumatic Fever. Hugh Ward.—p. 208.
Four Facets of Rheumatic Heart Disease in Paediatrics. M. L. Powell.—p. 210.
Accidental Poisoning in Childhood. F. W. Clements.—p. 211.
* A Social Study of Accidental Poisoning. Jean Allan and Howard Williams.—p. 213.
Accidental Poisoning in Childhood. John Beveridge.—p. 216.
Some Aspects of Diabetes Mellitus in Childhood. S. E. J. Robertson.—p. 218.
The Syndrome in the Infant Resulting from Maternal Emotional Tension During Pregnancy. Elizabeth K. Turner.—p. 221.
Undescended Testis: When and Why to Operate. A. Murray Clarke.—p. 222.
Childhood Schizophrenia. John F. Williams.—p. 224.
The Diagnosis of Haemorrhagic States in Childhood. John H. Colebatch and Betty M. Wilson.—p. 226.
Infectious Lymphocytosis. Douglas Galbraith.—p. 230.
Megaureter. F. Douglas Stephens. p. 233.
The Wringer Injury. David L. Dey.—p. 234.
Splenoptosis in Infancy: Two Cases. S. P. Bellmaine.—p. 236.

1:305-344 (Feb. 25) 1956

* Pre-Operative and Post-Operative Management of the Newborn: Introduction and Surgical Considerations. J. Steigrad.—p. 314.
* Pre-Operative and Post-Operative Care of the Newborn. A. Distin Morgan.—p. 315.
* Pre-Operative and Post-Operative Care of the Newborn. John Beveridge.—p. 316.
(All three articles are reviewed as a single article.)

1:345-388 (March 3) 1956

Stress in Childhood. D. R. MacCalman.—p. 355.
Stress in Children: The Study of a Group of Pre-School Children. F. W. Clements.—p. 357.

1:389-420 (March 10) 1956

* Penicillin-Resistant Staphylococci in the General Population. Phyllis M. Rountree and Judith Rheuben.—p. 399.
The Employment of Anaesthetic Principles in the Management of a Severe Case of Tetanus. B. W. Gunner, W. J. Cumming, and I. Schalit.—p. 402.

1:641-684 (April 21) 1956

Mycotic Infection of the Scalp: Mycology. E. Beatrix Durie.—p. 648.
* Neonatal Infection of the Skin by Staphylococcus Pyogenes. A. J. R. Clarke, A. H. McGeoch, and G. R. Sippe.—p. 655.
Tay-Sachs Disease: Report of Three Cases in One Family. R. Hertzberg.—p. 664.

1:685-728 (April 28) 1956

On the Management of the Juvenile Sex Offender. H. M. North.—p. 685.

1:817-860 (May 19) 1956

Immunization Against Poliomyelitis. P. L. Bazeley.—p. 821.
Gastro-Enteritis in Infancy and Childhood: A Review of 235 Cases. Hardjowinjono Goepito.—p. 836.

1:861-904 (May 26) 1956

Ten Years' Obstetrics in a Country Private Hospital. Paul Hopkins.—p. 866.
* Immunization of Children Against Whooping-Cough with Pertussis Haemagglutinin (H. A. P. A.): Field Results over Three Years. D. W. Rankin and S. Fisher.—p. 873.
The Practical Management of Intravenous Fluid Therapy in Infancy and Childhood. John Beveridge.—p. 875.
Immunization by the Blood Antigen Kell in Haemolytic Disease of the Newborn and in Blood Transfusion. R. T. Simmons.—p. 877.

A Social Study of Accidental Poisoning.—It is interesting to compare the social studies of accidental poisoning in children in Australia with similar studies in the United States. The present study concerns 419 children who attended a children's hospital in Melbourne. The commonest type of poisoning consisted of medications which were taken by 193 of the children. Sedatives and acetylsalicylic acid (aspirin) were the commonest. Substances of common household use were ingested by 174 of the children. The commonest of these substances was kerosene. Next in order were turpentine, caustic soda, and furniture polishes. Among the miscellaneous poisons insecticides and paints were the greatest offenders. The poisons were taken spontaneously in the vast majority of cases. In only 15 cases was the poison given by another child, and in only 9 cases was it given by accident in place of another medicine or tonic. The highest age incidence was from 1 to 3 years with a very small number in the age group from 3 to 15 years. It is interesting to note that among the medicines ingested 62% were in tablet form. Sixty-three per cent of the children from good homes as classified by the investigators, and seventy-nine per cent of the fathers were professional or businessmen or skilled tradesmen. Thus, the smaller number came from poorer families belonging to the labor groups with a lower standard of living. It was felt that true negligence on the part of the parents is an uncommon cause of the poisonings, and that three important factors emerge from this study: First, most of the children who take poison are active and curious; second, most of the substances ingested are easily accessible to the children; third, it is not realized by the parents that a number of common household substances are poison. The authors conclude that education of the parents along these lines is very important and that suitable storage and labeling of all poison substances must be accomplished.

Pre-Operative and Post-Operative Management of the Newborn: Introduction and Surgical Considerations; Pre-Operative and Post-Operative Care of the Newborn; Pre-Operative and Post-Operative Care of the Newborn.—The authors stress that improvement in the management of surgery of the newborn infant depends upon a number of factors. Early recognition of surgical conditions is of the utmost importance. General practitioner, pediatrician, and surgeon all must share in this factor.

Surgical technique is discussed, and it is believed that sedation is usually unnecessary. Atropine is used both to protect the child from excessive secretion and to lessen reflex vagal effects. Ether is considered the best anesthetic agent, though others may be used for their special properties. Relaxants without anesthesia have been successfuly used. Intubation is often advisable for the best possible respiratory control. Whatever drugs are used the dose should be minimal, the airway should be free, and oxygen should be maximal. Gastric intubation is performed as early as possible when abdominal distention is present. Preoperative blood transfusion is rarely needed except when blood loss has taken place. Dehydration may be a problem, but the authors state that more frequently they see infants who are overhydrated by the overzealous administration of saline.

Postoperative shock may be difficult to recognize by those unfamiliar with the problem in the newborn. Slow heart rate, pallor, and subnormal temperature are frequent signs of shock. Abnormal respiratory pattern may also be present. Fluid given will consist of that necessary for maintenance needs and to replace fluid loss from suction. One author uses a one-eighth strength saline solution in 5% dextrose for maintenance solution and a half strength saline in dextrose for replacement solution. Potassium is given only when loss by suction is relatively great. Protein, as human albumin, is given daily in an amount to supply 1 gm. per kilogram of body weight. Alimentary-tract feeding is undertaken as early as possible.

Penicillin-Resistant Staphylococci in the General Population.—In a survey of 200 blood donors carried out in Sydney, Australia, in December, 1955, one-half of these subjects were carriers of Staphylococcus aureus as determined by nasal swab technique. Twenty-five per cent of these carriers had a strain of the organism which was resistant to penicillin. This was double the number found in a similar study carried out 20 months previously. Of 85 staphylococci strains isolated from various superficial lesions occurring in private patients and those seen as out-patients in the hospital, 63.5% were resistant to penicillin. The main points of interest in the survey were the increase in nasal carriers of penicillin-resistant staphylococci among blood donors in Sydney and the high incidence of resistant organisms isolated from the superficial infections. The authors stress that there may be seasonal and geographical variations in the occurrence of such organisms, but it is implied that the therapeutic and prophylactic efficiency of penicillin in staphylococcal infections is diminishing.

Neonatal Infection of the Skin by Staphylococcus Pyogenes.—Investigations of infections of the skin in 200 newborn infants at the Maitland Hospital showed an incidence of 21.5%. In part the high incidence is attributed to the careful observation for skin infections and that some of these lesions might have been overlooked in other circumstances. It is not clear whether all of these were due to staphylococcal organisms; however, when this specific organism was isolated it was found to be penicillin-resistant and belonged to phage type 80 (Rountree). During a 15-week period there was no reduction in the incidence of infection among the newborn infants with very careful attention to nursing standards. Investigation of the bacterial flora of the nurses' anterior nares revealed two carriers of penicillin-resistant Staphylococcus aureus phage type 80. These nurses were treated with a 1% oxytetracycline ointment inserted 3 times daily into the nose. This procedure resulted in a pronounced and lasting reduction in the incidence of neonatal skin infections.

Immunization of Children Against Whooping-Cough with Pertussis Haemagglutinin (H.A.P.A.): Field Results over Three Years.—H.A.P.A. is a suspension of floccules of aluminum phosphate on which are absorbed components of freshly grown virulent Hemophilus pertussis obtained by extracting bacterial bodies with molar, slightly alkaline sodium chloride solution. The immunizing course for children in this study consisted of two injections of 0.25 ml. given a month apart. This report concerns the results of a three-year study. In one investigation information obtained from practitioners concerning home contacts of children revealed that only 2 contracted pertussis of 19 immunized with H.A.P.A.; 14 out of 16 children who were not immunized contracted the disease. In a second investigation concerning municipal districts 9 cases of pertussis were found in 4920 child-years in children immunized with H.A.P.A.; 204 cases occurred in 30,063 child-years in nonimmunized children. The ratio of these studies is roughly 1:500 as compared with 1:150. These results are considered to show that H.A.P.A. is an effective prophylactic.

Medizinische Klinik, Berlin

51, No. 20 (May 18) 1956

Pathology and Therapy of Disorders of Nutrition. F. Thoenes.—p. 845.

51, No. 21 (May 25) 1956

(This number deals with various aspects of pain)

The Bodily Fundaments of Pain. F. Erbslöh.—p. 877.
The Problem of Pain in Internal Medicine. H. Ley.—p. 884.
Pain from the Surgical Viewpoint. H. Hellner.—p. 889.
Operative Relief of Pain. T. Riechert.—p. 895.
Pharmacological Problems in the Relief from Pain. O. Schaumann.—p. 901.
Psychotherapy of Pain. W. Th. Winkler.—p. 905.
Pain as Symbol. A. Mitscherlich and G. Ruffler.—p. 909.
Medical Anthropology of Pain. M. Mikorey.—p. 914.
The Meaning of Pain. H. Fleckenstein.—p. 917.

51, No. 22 (June 1) 1956

The Classification of Anemias According to Newer Points of View and its Advantages: Part I. M. A. Roemer.—p. 931.
* Tubeless Determination of Stomach Juice with Desmoid Pills "Pohl." W. Lutz.—p. 936.

51, No. 23 (June 8) 1956

The Classification of Anemias According to Newer Points of View and Its Advantages: Part II. M. A. Roemer.—p. 976.

51, No. 24 (June 15) 1956

ACTH Treatment of Nephrosis in Children. W. Kosenow and P. Hallermann.—p. 1024.

51, No. 25 (June 22) 1956

The Fundamentals of Specific Prophylaxis of Poliomyelitis. C. W. Jungeblut.—p. 1053.
Roentgen Examinations of the Head in Neuroendocrinopathics and Distrubances of Growth. N. Pende and V. Pende.—p. 1058.

51, No. 26 (June 29) 1956

Sigmavolvulus in Childhood. E. Smola.—p. 1100.

Vol. 51, No. 27 (July 6) 1956

Observations from a Vacation Camp for Diabetic Children and Adolescents. W. Lanzenderfer.—p. 1145.

Tubeless Determination of Stomach Juice with Desmoid Pills "Pohl."—A small rubber bag is filled with methylene blue and firmly closed by a desmoid (catgut) thread. When sufficient pepsin and hydrochloric acid is secreted the thread is digested and the urine becomes green or blue, normally within three-four hours. The appearance of the dye in the urine was checked by the usual determination of hydrochloric acid in juice obtained by gastric tubes at various intervals after a test consumption of pure caffeine. In the absence of free hydrochloric acid no dye is liberated, with an agreement of 96%. It happens rarely that in spite of the presence of free acid no dye appears in the urine or dye appears in spite of absence of free acid. It is recommended to give the desmoid pill "Pohl" during breakfast. The test seems to decide whether an anacidity exists or not and can replace the fractionating aspiration of stomach juice in praxis.

The Fundaments of Specific Prophylaxis of Poliomyelitis.—The importance of tissue immunity in contradistinction to humoral antibody immunity is stressed, although some significance if conceded to these. It may be noted that the figures given for the Massachusetts poliomyelitis epidemic with reference to the morbidity of children vaccinated with Salk vaccine and those not vaccinated have been exchanged, while the percentage reduction of the morbidity of the vaccinated remains correct. The author concludes that the reports registering the results obtained by Salk vaccine prophylaxis have been too optimistic.

Metabolism, New York

5, No. 4 (July) 1956

Symposium: Water and electrolytes.
* The Role of Aldosterone in Normal Homeostasis and in Certain Disease States. F. C. Bartter.—p. 369.
Electrolyte Changes in Renal Failure. J. P. Merrill.—p. 419.
The Skeleton as an Electrolyte Resevoir. W. H. Bergstrom.—p. 433.
Body Composition. F. D. Moore, J. D. McMurrey, H. V. Parker, and I. C. Magnus.—p. 447.
Interpretation of the Serum Potassium Concentration. B. H. Scribner and J. M. Burnell.—p. 468.
Water Intoxication and Serum Hypotonicity. V. Wynn.—p. 490.
The Pathogenesis of Hyponatremia: Physiologic and Therapeutic Implications. I. E. Edelman.—p. 500.
Hypernatremia. H. C. Knowles.—p. 508.

The Role of Aldosterone in Normal Homeostasis and in Certain Disease States.—Aldosterone has finally been identified as the steroid responsible for sodium retention and potassium loss. The steroid is analogous in action to desoxycorticosterone the physiological importance of which in normal homeostasis is questionable. Presumably aldosterone is concerned with hydrogen-ion transport by the kidney and when present in excess alkalosis may result. Its secretion is largely independent of ACTH.

Aldosterone is excreted in the urine in excess in edema states, such as cirrhosis, nephrosis, and congestive heart failure. The reason for this increased secretion is not apparent. Primary hyperaldosteronism is a syndrome resulting from an aldosterone-producing tumor. In the few patients in which the diagnosis has been confirmed by exploration, hypokalemia, alkalosis, hypertension, paralysis, tetany, and polyuria were present. Strangely, edema was absent. Primary hyperaldosteronism can be distinguished from secondary hyperaldosteronism by the fact that in the former, when dietary sodium is reduced, sodium virtually disappears from the urine.

Monatsschrift für Kinderheilkunde, Berlin

103, No. 12 (Dec.) 1955

* X-Ray Diagnosis of Intracranial Calcification in Childhood. G. Arzt and N. Schad.—p. 501.
* Marked Changes in the Cellular Components of Bone Marrow in Children with Tuberculosis: Behavior of the Peripheral Blood After Prolonged Treatment with Iso-Nicotinic Acid Hydrazid in Large Doses (Using the Hungarian Preparation "Isonicid K. Gy."). O. Lombos, M. L. Radek, and L. Szoenyi.—p. 508.

Hydrocephalos and Lacunar Skull with Spina Bifida. Hans Schoenenberg.—p. 514.
Normal X-Ray Variations and Pathological Changes of the Sternal Portion of the Clavicle. R. Ottenjann.—p. 516.
Ichthyosis Congenita. Friedrich Eckardt and Ernst Born.—p. 518.
Oral Penicillin in the Home Treatment of Scarlet Fever. Alexander Sinios.—p. 522.
The Respiratory System: Review Article. H. Hilber.—p. 523.

105, No. 1 (Jan.) 1956

Blood Coagulation of the Newborn Infant. Harold Haupt.—p. 1.
Differential Diagnosis of Atelectasis of the Right Lung, Especially in Regard to Agenesis. Helmut Karte.—p. 6.
* Erythroblastemia of the Newborn Infant: A Morphological Study of the Differential Diagnosis of Erythroblastosis Fetalis with Special Emphasis on Post-Hemorrhagic Shock of the Newborn. Fr. Koch, K. Schlagewetter, and W. Schneidt.—p. 11.
* Use of Bromsulphalein in the Diagnosis of Liver Function in Children. F. H. Dost and T. Goetze.—p. 22.
The Epidemiology of Epidemic Vomiting: Report of 191 Cases. G.-A. v. Harnack.—p. 26.
Blood and Blood-Forming Organs: Review Article. Klaus Seelemann.—p. 32.

104, No. 2 (Feb.) 1956

Epidemiological and Serological Studies of Interstitial Plasma-Cell Pneumonia of Premature Infants. E. Reisetbauer and H. Moritsch.—p. 41.
Determinations of Size and Form of the Sella Turcica in Children up to 14 Years of Age. Armin Unterberg.—p. 46.
The X-Ray Significance of Air Content in the Small Intestine in Pylorospasm. W. Schermuly.—p. 50.
* Cytometric Studies of the Course of the Epithelial Pregnancy Reaction of the Newborn. B. Leiber and I. Henschel.—p. 52.
A Simple Method for the Determination of Pediatric Doses of Medications. G.-A. v. Harnack.—p. 55.
The Influence of Non-Specific Factors on the Appearance of Tuberculin Reactions Close to the Site of BCG Vaccination. Kurt Lother.—p. 56.
* Treatment of Childhood Tuberculosis with P-Amino-Salicylic Acid Salt of Isonicotinic Acid Hydrazid. F. Ferlinz.—p. 60.
Treatment of Spastic-Hypertrophic Pyloric Stenosis with Phenothiazine Mixtures. L. Arp and W. Leuterer.—p. 64.
Inner Secretions: Review Article. Kurt Nitsch.—p. 67.

X-Ray Diagnosis of Intracranial Calcification in Childhood.—Intracranial calcification in childhood is divided into the following groups on the basis of x-ray findings:

1. Physiological calcifications without clinical or pathological significance.
   (a) Calcification of the pineal gland in its normal location.
   (b) Calcification of the falx cerebri in its normal location.
   (c) Calcification of the choroid plexus in its normal location and with normal configuration.
   (d) Calcification of bands in the region of the petrosal sella.
   (e) Calcification of Pacchionian granulation bodies.
   (f) Dystrophic calcification without clinical symptoms.
2. Pathological calcification.
   A. Physiological calcification at abnormal sites.
      (a) Pineal gland.
      (b) Falx cerebri.
      (c) Choroid plexus.
   B. Tuberculosis.
      (a) Tuberculoma.
      (b) Meninges.
   C. Tumors.
   D. Intracranial hemorrhage including those due to birth trauma.
   E. Toxoplasmosis.
   F. Sturge-Weber syndrome.
   G. Tuberous sclerosis.
   H. Calcified parasites.
   I. Epilepsy.
3. Extraneous objects confused with hyperostosis or calcification, i.e., dyed hair, braids, head-supporting structures, hair pins, etc.

Marked Changes in the Cellular Components of Bone Marrow in Children with Tuberculosis: Behavior of the Peripheral Blood After Prolonged Treatment with Iso-Nicotinic Acid Hydrazid in Large Doses (Using the Hungarian Preparation "Isonicid K. Gy.").—Twenty-three children, ranging in ages from 8 months to 12 years, of whom fifteen had tuberculous meningitis, three miliary tuberculosis, and five pulmonary tuberculosis, were treated with isonicotinic acid hydrazid for 7-8 months. Preparation used was "Isonicid K. Gy.," a Hungarian drug. Dose used was 15 mg/kg/day.

Twenty-two of these patients exhibited bone-marrow lymphocytosis of 55% at the conclusion of therapy. Lymphocytosis of peripheral blood was found in 12 patients. No correlation between peripheral blood and bone-marrow lymphocytosis was noted in 50% of the patients. Age, that is the younger age groups being more affected, seemed to play a strong role in the occurrence of blood lymphocytosis, less so in bone-marrow lymphocytosis.

Bone-marrow lymphocytosis was considered a favorable prognostic sign because

(1) it occurred also in untreated cases,
(2) in a child with poor outlook, lymphocytosis disappeared despite treatment with isoniazid,
(3) all patients who exhibited bone marrow lymphocytosis were cured,
(4) hemoglobin and red blood cell counts rose, whereas peripheral lymphocytosis dropped.

Blood lymphocytosis was also found to be a favorable prognostic sign.

Erythroblastemia of the Newborn Infant: A Morphological Study of the Differential Diagnosis of Erythroblastosis Fetalis with Special Emphasis on Post-Hemorrhaghic Shock of the Newborn.—In the last few years there have been reported a number of cases of erythroblastosis fetalis not due to antigen-antibody reactions but due to as yet unknown causes.

Blood group serology does not provide the answer. Thorough and systematic morphological studies of blood and bone marrow gave the following conclusions:

Morphological examination of bone marrow served to differentiate typical cases of erythroblastosis fetalis from atypical cases. A patient with posthemorrhagic shock of the newborn due to occult bleeding into the maternal circulation was studied and it was possible to differentiate this entity from erythroblastosis fetalis due to antibody reactions.

In typical cases of erythroblastosis fetalis examination of the bone marrow was found to be a better index of the severity of the disease than serologic determinations of the antibody titers.

Use of Bromsulphalein in the Diagnosis of Liver Function in Children.—Bromsulphalein excretion of healthy children and of children with liver diseases were determined using the half-time-value method.

Children without liver disease were found to have values of 3.1 to 6.1 minutes, those with liver disease of various varieties had statistically significantly higher values.

Values for children and adults were found to be comparable without conversion.

Cytometric Studies of The Course of the Epithelial Pregnancy Reaction of The Newborn.—Using serial cytometric studies of vaginal and oral epithelium of 100 newborn infants of both sexes, it was possible to determine the exact duration of the epithelial pregnancy reaction.

It could be stated unequivocably that syncoiogenetic influences on epithelium were concluded at the end of the first two weeks of life. Changes of the vaginal mucosa were found to be more marked than those of the oral mucosa; however, the latter were distinct enough to yield usable results even in small infants. Epithelium of both sexes exhibited the same behaviour as regards quality, quantity, and time.

These changes occurring by the second week of life were statistically so significant that they could be used to determine age not only forensically but also to corroborate biologically the conclusion of the newborn period.

Treatment of Childhood Tuberculosis with P-Amino-Salicylic Acid Salt of Isonicotinic Acid Hydrazid.—P-amino-salicylic salt of isonicotinic acid hydrazid ("DIPASIC") administered orally was found to possess strong tuberculostatic properties and was tol-

erated extremely well. Results of its use in 33 tuberculous children, ages ranging from 20 months to 15 years, were comparable with those obtained with combined therapy using streptomycin and para-aminosalicylic acid or streptomycin and isonicotinic acid hydrazid. These patients had either epituberculosis or postprimary lymph-hematogenous spread. No toxic side-effects were noted.

The drug was used for cases in which combination therapy was not tolerated. Dose was at least 20 mg/kg/day in three divided doses; therapy was continued until a total of 40 to 50 gm. had been administered.

New England Journal of Medicine, Boston

254, No. 18 (May 3) 1956

Mitral-Valve Disease: A Radiologic Approach to a Physiologic Diagnosis. James B. Dealy Jr.—p. 825.
Physiologic Changes in Mitral Stenosis. Lewis Dexter.—p. 829.
Late Follow-Up Study of Radiologic Changes After Mitral Valvuloplasty. John E. Gary.—p. 831.
Some Surgical Aspects of Mitral Stenosis. Dwight E. Harken.—p. 835.
Urinary-Tract Malformations: Their Familial Occurrence, with Special Reference to Double Ureter, Double Pelvis and Double Kidney. Leonard S. Girsh and N. E. Karpinksi Jr.—p. 834.
* A Second Outbreak of Boston Exanthem Disease in Pittsburgh During 1954. Franklin A. Neva.—p. 838.

254, No. 19 (May 10) 1956

Organized Thrombus Occluding a Main Pulmonary Artery—Report of 2 Cases. S. L. Laufer and J. D. Gray.—p. 893.
* A Statistical Appraisal of the Serum Protein-Bound Iodine As a Test of Thyroid Function. Morris E. Dailey and J. Richard Skaden.—p. 907.

254, No. 20 (May 17) 1956

* Effect of Penicillinase on Circulating Penicillin. Robert M. Becker.—p. 931.

254, No. 21 (May 24) 1956

* Psychiatric Considerations in the Adjustment of Patients with Poliomyelitis. H. A. Robinson, J. E. Finesinger, and J. S. Bierman.—p. 975.
Treatment of Chronic Granulocytic Leukemia with 1,4-Dimethanesulfonyloxybutane (Myleran). Robert F. Schilling and Ovid O. Meyer.—p. 986.

254, No. 22 (May 31) 1956

Osteomalacia of Unknown Etiology. W. E. Segar, F. L. Iber, and L. H. Kyle, with the technical assistance of Natalie Lawson and Betty Hackley.—p. 1011.
* Renal Function After Recovery from Acute Renal Failure. J. T. Kirkenstaedt and J. P. Merrill.—p. 1023.
Adrenocortical Steroids and Tuberculosis: A Reminder. I. M. Golding, W. Lester, and G. S. Berg.—p. 1026.
Medical Progress: Regional Enteritis. L. Zetzel.—p. 1029.

254, No. 23 (June 7) 1956

* Disseminated Pulmonary Calcification: Its Association with a Positive Reaction to Histoplasmin Antigen. Mark H. Joress and Boris P. Busliueff.—p. 1053.
Fluoridation of Water Supply: The Norway, Maine Study. Alonzo H. Garcelon.—p. 1072.
Arthritis Research. C. B. Favour, Roy E. Ritts Jr., and Theodore B. Bayles.—p. 1078.

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Experience with the Use of Chlorpromazine and Reserpine in Psychiatry: With Especial Reference to the Significance and Management of Extrapyramidal Dysfunction. George W. Brooks.—p. 1119.
* Hereditary Hematuria, Nephropathy and Deafness. George S. Sturtz and Edmund C. Burke.—p. 1123.
Syphilis and Its Management: A Present-Day Problem. Nicholas J. Fiumara, Bernard Appel, William Hill, and Herbert Mescon.—p. 1127.

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* Urticaria Pigmentosa As a Problem in Diagnosis (Report of Two Cases, One with Systemic Involvement). P. Brodeur and Lytt I. Gardner.—p. 1165.
Syphilis and Its Management: A Present-Day Problem (Concluded). Nicholas J. Fiumara, Bernard Appel, William Hill, and Herbert Mescon.—p. 1173.
Lead Poisoning After Ingestion of a Foreign Body Retained in the Stomach. Major Frederick C. Biehausen and Lt. Col. Edwin J. Pulaski.—p. 1179.

254, No. 26 (June 28) 1956

* Serum Protein Alterations in Uremia: II. Elevated Alpha-2 Globulin in Patients. Alex L. Finkle, Joel F. Panish, Sara S. Karg, and Donald R. Smith.—p. 1203.
Some Abuses of Drugs in Therapy. Dale G. Friend and George A. McLemore Jr.—p. 1223.

A Second Outbreak of Boston Exanthem Disease in Pittsburgh During 1954.—The author reports an outbreak in a community with some scattered cases from other parts of the city of an exanthem similar to that previously reported in Boston in 1951. The children generally manifested fever, lasting about two days, headache, sore throat, stomach ache and poor appetite. A pink maculopapular rash, more prominent on face, chest, back, and buttocks appeared, usually after the temperature became normal, although sometimes during the fever. In most cases the mothers noted a redness of the eyes at the onset. Adults were much more prostrated with chills, severe muscular aches, and burning and pain in the eyes. Many patients had redness of the pharynx. Some had a few tiny, yellow-white, raised lesions on soft palate or uvula. Specimens from 18 of 19 patients grew out a cytopathic agent, mostly from stools; there were also positive cultures from throat washings. In 14 of 16 tests for neutralizing antibodies to the agent, a fourfold or greater rise in neutralizing antibody titers in convalescent phase serum, as compared with acute phase serum, was demonstrated. The clinical picture and virus studies were compared with the Boston epidemic and found quite similar.

A Statistical Appraisal of the Serum Protein-Bound Iodine as a Test of Thyroid Function.—This is a study on adults which was designed to ascertain the usefulness of the determination of the serum protein-bound iodine as a gauge of thyroid function. No tests were done on anyone who had had organic iodine or on anyone who had had inorganic iodine within the last two months. No pregnant women were included. There were a total of 804 euthyroid cases, including 313 controls, 126 with anxiety state, 44 with obesity, 96 with a readily palpable gland (no evidence of thyroiditis), 141 who had undergone thyroidectomy, 49 who had received radioactive iodine for Grave's disease, and 35 who required thyroid (dessicated) to remain euthyroid. All of these patients were considered clinically as euthyroid. These values were compared with known hypo- and hyperthyroid cases. The mean value for the euthyroid was 6.16 with a range of just below 4 to 8.7; that for the hypothyroid was 3.58 with a range up to 5; that for the hyperthyroid was 11.44 with a range as low as 6. The authors felt that the test was not too valuable in diagnosing hypothyroidism if 4.0 is set as the low limit of normal; they did feel that elevated values were significant and made the diagnosis of hyperthyroidism highly probable.

Effect of Penicillinase on Circulating Penicillin.—Penicillinase was injected into guinea pigs and also humans with no evidence of toxicity. In humans, after consistent blood levels were established for several days by a twice-a-day injection of fortified procaine penicillin of 800,000 units each, a single injection of 100,000 to 800,000 units of purified penicillinase was given intramuscularly. Within an hour and for periods of four to seven days later, no circulating penicillin could be detected despite the fact that the injections of penicillin were continued twice a day.

Psychiatric Considerations in the Adjustment of Patients with Poliomyelitis.—This is a preliminary study of children with poliomyelitis. These children had spinal poliomyelitis, all with some degree of lower-extremity involvement. The study is designed to investigate some of the circumstances or factors that appear to contribute to the way patients and their families react and adjust to the total experience of the disease and its sequelae. Some observations follow. The authors noted that, in spite of the publicity, the people still had a very varied and often bizarre notion as to the way in which the disease was contracted. The authors also noted that these children were very compliant to immotility, a fact which they attributed to guilt feelings. After discharge of the patient, parenteral influence becomes a big factor in the progress of the patient. Another fact the authors report is that the patients have very little to say about their physician. The physical therapist is the person who is usually prominent in the minds of the patients. This was thought due to the fact that the patient saw so

little, comparatively, of their physician. The authors support their points with examples. They expect the study to take about two years.

Renal Function After Recovery from Acute Renal Failure.—This paper records another long-term follow-up of 16 patients who recovered from acute renal failure. There were patients who had no known evidence of cardiovascular or renal disease before the acute episode. In 10 patients more than one follow-up observation was done. Specific gravity was determined after a 12-hour period of withholding water, a value of 1.024 being considered normal. Constant infusion rates of inulin and para-aminohippuric acid solutions were maintained by an infusion pump. The bladder was catheterized. Clearance values were the average of four or more periods. After the clearance studies, a 15-min. P. S. P. was done.

All patients made an excellent clinical recovery from the acute episode and were in good health except one (periarteritis nodosa developed in this patient). By six months the specific gravity and P. S. P. were normal, but clearance studies showed subnormal values for many months in most of the cases. This was thought consistent with permanent renal damage of mild degree. It was stated that when oliguria had been associated with recurrent episodes of hypotension and infection, more chronic renal damage has resulted. It was also stated that after recovery from acute renal failure, progressive diminution of renal function does not occur unless some other disease causes additional renal damage.

Disseminated Pulmonary Calcification: Its Association with a Positive Reaction to Histoplasmin Antigen.—The authors call attention to the many reports in the literature relating the presence of disseminated pulmonary calcification to positive skin tests for histoplasmin sensitivity. Although the greatest incidence is in the Mississippi River Delta area, there are other point sources of infection throughout the country. The authors call attention to the fact that excreta from chickens, pigeons, and bats is often the source of the fungus and that an acid soil appears best suited for its growth.

In the 20 cases the authors reported, 10 were from the epidemic areas, whereas the other 10 were from the East (Mass., Pa., R. I.). Only 10 of the 20 had histories of respiratory infections. Most of the x-rays were diagnosed as some form of healed tuberculosis, from miliary to healed primary complex. Only 1 of the 15 sera studied showed a positive test for antibodies.

In the acute phase of the disease, initial x-rays usually show a bronchopneumonia type of infiltration, usually diffusely scattered and predominantly at the base, often involving the lymph nodes. In healing, these areas develop calcium in them.

Complement-fixation and precipitin tests usually show high titers within three months but titers fall thereafter, especially precipitin titers.

Differential diagnosis is discussed—tuberculosis, coccidioidomycosis, other fungi, hamartoma and other primary or metastatic tumors.

The authors suggest that the clinician and roentgenologist should have a high degree of suspicion if the diagnosis of histoplasmosis is to be made more frequently.

Hereditary Hematuria, Nephropathy and Deafness.—This is a report of a familial renal disease associated with nerve deafness. Three criteria are necessary for the diagnosis:

1. A family history of progressive renal disease in males affected.

2. The presence or history of hematuria which may be intermittent.

3. Nerve deafness in most of the males and some of the females affected (involvement of auditory nerve or organ of Costi).

A brief case history is given illustrating the clinical findings and the inheritance in the family tree. The authors could find only two other reports in the literature each dealing with one family tree that seemed to correspond to the same disease. All these were in Anglo-Saxons. They found one incomplete report of the possibility of the disease in a Jewish family.

The authors also state that the females do not usually have progressive renal disease but that they may get into trouble during pregnancy with the development of hypertension, edema, and toxemia.

Urticaria Pigmentosa As a Problem in Diagnosis (Report of Two Cases, One with Systemic Involvement).—This is a report of two cases of a rare disease. The first case developed "ecchymoses" at age 3 months. Blood picture normal. He continued to have these lesions and at the age of 17 months the diagnosis was made. At this time the lesions were brownish yellow macules and papules. Rubbing the lesions produced a wheal. The second case developed a rash at age 2 months—generalized, erythematous, and characterized by itching. Also marked dermatographia was noticed. At 9 months a skin biopsy was read as negative. At 5 years he was seen again with widespread, pale erythematous rash. He had hepatomegaly, appeared chronically ill and had a tendency to bleed easily. Bone marrow revealed mast cells, and a restraining of original skin biopsy revealed mast cells (missed with the usual hematoxylin and eosin stain).

The authors discuss the significance of mast cells which are found in this disease in large numbers. There is strong evidence that mast cells contain extraordinary concentrations of heparin and histamine. The authors demonstrated enormous values of histamine and heparin-like substance in the liver of the second case. The authors suggest that the disease is caused by a congenital inadequacy of an enzyme involved in the degradation of histamine or of heparin. They further suggest that the proliferation of mast cells may be a homeostatic reaction to provide an intracellular storage place for these compounds. They further suggested that, since cortisone was shown to cause marked regression of mast cell tumors in dogs, it be tried in this disease.

Serum Protein Alterations in Uremia: II. Elevated Alpha-2 Globulin in Patients.—The authors demonstrated an "unequivocal, consistently elevated" alpha-2 globulin in 73% of 45 patients with uremia from various causes. This finding was most consistently related to parenchymal functional impairment. It varied with changes in the course of the disease and could be used as a prognostic sign. It was thought to indicate a fundamental alteration in protein metabolism. This same finding may be seen in cardiac, hepatic, and nephrotic illnesses, some skin diseases and some malignant tumors (including Hodgkin's). The cause of the alteration of the protein pattern is unknown.

Pédiatrie, Lyon, France

43, No. 7, 1955

* Prognosis of Tuberculous Meningitis by Electroencephalography (A Study of 400 Tracings). Ch. Sarrouy, Mme. Saint-Jean, and L. Sendra.—p. 697.
* Myeloplaxoma of the Synovial Membrane of the Knee in Children. M. Salmon, Corti, and Aubrespy.—p. 703.
* Massive Gangrene of the Extremities in Infants. J. Roget, A. Beaudoing, and P. Moulin.—p. 721.
* Strabismus in Children Complicated by Neuropsychiatric Conditions: Preliminary Study.—p. 753.

Prognosis of Tuberculous Meningitis by Electroencephalography (A Study of 400 Tracings).—Whereas a normal or grossly disturbed electroencephalogram at the onset of the illness in indicative of good or bad prognosis, tracings which are only moderately abnormal can be interpreted prognostically only if their evolution is studied over a period of time.

The patients were classified into three groups: (1) where the electroencephalogram remained uniformly good, indicating a good prognosis, although the changes of the cytological findings in the liquor were not consistent; (2) where persistent changes of the electroencephalogram to the worse indicated a poor prognosis (borne out by the death of the patients) although the cytological findings were improving and thus misleading; ie the third group (3) moderately abnormal electroencephalographic tracings improved rapidly, whereas the cellular findings fluctuated over a longer period of time; ultimately the patients recovered. In this group the cytological findings seemed more sensitive than the electroencephalogram.

Myeloplaxoma of the Synovial Membrane of the Knee in Children.—Two cases of myeloplaxoma in 12- and 13-year-old girls were treated successfully by x-ray therapy and surgery.

The authors warn of misdiagnosis of tuberculosis in these cases and recommend biopsy.

Massive Gangrene of the Extremities in Infants.—In the special section, "General Review," the authors thoroughly discuss all aspects of the subject, cite three of their own observations, and refer to four and a half pages of references from the world literature.

Strabismus in Children Complicated by Neuropsychiatric Conditions: Preliminary Study.—The authors wish to stimulate interest in this frequently mentioned but unstudied field. Among the neurological conditions coincidental to strabismus found in random samples from an eye clinic, they discovered Mongolism, encephalopathies, microcephalus, head injury with facial paralysis, and convulsions. Among the psychiatric conditions they found character disturbances, two cases of psychogenic strabismus—one aggravated after the suicide of the mother, another occurring after the birth of an unwanted sister. Among the cases classified as psychosomatic the authors list corrected left-handedness, enuresis, stuttering, tics, dyslexia, and anorexia.

La presse médicale, Paris

64: Jan.-March, 1956

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A New Treatment for Amebiasis: Mercaptoarsenical. A. Ravina.—p. 29.
* Isoniazide and Pregnancy. Pierre Aboulker and S. Muhlrad.—p. 45.
* Cerebral Hemispherectomy for Infantile Hemiplegia. D. Ferey.—p. 81.
* Spontaneous Pneumothorax, Mediastinal and Subcutaneous Emphysema in the Asthmatic Patient. J. Turiaf, P. Marland, and H. Mathieu.—p. 125.
* A Factor of Mental Anorexia of Adolescence: Rejection of Material Needs as an Affirmation of "Pure Intellectualism." L. Michaux and L. Georges Janet.—p. 181.
Polyneuritis Due to Isoniazid. E. Benhamou and M. Timsit.—p. 199.
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* Treatment of Asthma with Predisone. P. Vallery-Radot, C. Laroche, and J. Bonnet de la Tour.—p. 273.
Preliminary Note on the Treatment of Leukemia by Metacortandracine (Eleven Cases). R. Picard, J. Horeau, J. Guinat, J. Guillon, M. Hardy, and J. Guepin.—p. 301.
Incidence of Color Blindness in France. R. Kherumian. C. Baudry, J. Lacorne, and J. Moullec.—p. 303.
* Psychasthenic Child. Jean Cathala.—p. 355.
Cardiac Localization Assuming the Form of Acute Pericarditis Due to Infectious Mononucleosis. J. Celice, F. Plas, A. Peltier, and S. Papazian.—p. 425.
* Nervous Manifestation of Infectious Mononucleosis. P. Rentchnick.—p. 473.
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Surgery in Patients with Bleeding Tendency. J. P. Soulier.—p. 499.
* Extra-Dural Hematomas of the Cerebellar Fossa. D. Petit-Dutaillis, G. Guiot, B. Pertuiset, and Y. Le Besnerais.—p. 521.
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Hydrocortisone in the Treatment of Chronic Maxillary Sinusitis in Children. R. Maspetiol, Grenet, J. Chauvet, and Desbois.—p. 530.
* Nervous Manifestations of Infectious Mononucleosis (II). Pierre Rentchnick.—p. 589.
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64: April 14, 1956

* Utility of Heparin in the Treatment of Lipoid Nephrosis. Y. Boquien, and J. F. Porge.—p. 689.

64: April 18, 1956

* Paper Electrophoreses: Critical Review. E. Azerad, J. Lewin, and J. Ghata.—p. 744.

64: April 25, 1956

Leontiasis Ossea in Children (Probably Partial Osteoporosis): Case Report. J. A. Lievre and H. Fischgold.—p. 763.
* Surgical Treatment of Pulmonary Stenosis Under Direct Vision. N. Oeconomos.—p. 776.

64: May 5, 1956

* Kala-Azar and the Nervous System (with Description of Two Cases of Epilepsy Occurring late in the Disease. P. Gallais and H. Collomb.—p. 846.
* Treatment of Childhood Schizophrenia. L. Michaux and Hubert Flavigny.—p. 846.

64: May 9, 1956

* First Experimental Results in France of Cardiac Surgery with the Oxygen-Pump system of Lillehei-DeWall. C. Lenfant, M. Weiss, J. Rouanet, R. DeWall, G. Nahas, C. Dubost.—p. 869.

64: May 19, 1956

Plastic Nursing Bottle and Prurigo Storphylus. G. Keridjian.—p. 933.

64: May 23, 1956

Dysembryoplastic Cyst of the Thymus: Case Report in a Child. H. Joly, F. M. Tobe, P. Lowys, and J. Lengrand.—p. 969.

64: June 20, 1956

Intrathecal Hydrocortrisone Therapy in Neurologic Disorders (26 Cases). R. Turon, R. Giacardy, and M. Garde.—p. 1133.

64: June 23, 1956

Enlargement of the Limits of the Pump-Oxygenator System of Lillehei-DeWall for Bloodless Cardiac Surgery: Experimental Study of Two Modifications Permitting the Application of Extracorporeal Circulations to the Adult. C. Lanfant, M. Weiss, J. Rouanet, and C. Dubost.—p. 1162.

64: July 4, 1956

* Treatment of Human Tuberculosis with Cycloserine. A. Ravina and M. Pestel.—p. 1241.

64: July 7, 1956

* Preliminary Note on the Oral Treatment of Diabetes with D 860 (*s*-(Sulfonyl-*p*-Methylbenzene) N-Butyl Urea). R. Moreau, R. Deil, A. Sarrazin, P. M. De Traverse, and M. Martinet.—p. 1261.

Adenoidal-Pharyngeal-Conjunctival Viruses, a New Group of Viruses Pathogenic to Man. P. Tournier.—p. 1256.

64: July 14, 1956

Variations in Plasma Proteins in the Course of Anuric Tubulonephritis. M. Derot, P. Pignard, and N. Legrain.—p. 13307.

Two Cases of Generalized Tetanus Successfully Treated by a Combination of Continuous Infusion of 3697 RP (Flaxedil) and Neuroplegic Mixtures. Turon, Garde, and Heches.—p. 1309.

Isoniazid and Pregnancy.—Three pregnant women with renal tuberculosis were treated throughout pregnancy with INH combined with streptomycin and PAS. Three normal infants were born.

Cerebral Hemispherectomy for Infantile Hemiplegia.—The author reports 10 cases age 4 through 20 years personally operated upon since July 1953, by removal of entire hemisphere, leaving the caudate nucleus, thalamus, and in some cases the lenticular nucleus with their blood supply. Of the 10 cases, all had hemiplegia or hemiparesis, 7 had severe epilepsy, 8 had severe behavior disorders obscuring their actual intelligence, and 3 were idiots. Of the eight who survived operation, results to date (follow-up 3 to 26 months) are highly encouraging: disappearance or great improvement of the hemiplegia, (although hand function may be made worse), improvement in behavior, disappearance of seizures, and improvement in useful intelligence. The authors suggest that in selected children with brain damage, if the contralateral hemisphere is intact, hemiplegia, severe epilepsy, severe behavior disorder, or mental deficiency may be indications for hemispherectomy.

Spontaneous Pneumothorax, Mediastinal and Subcutaneous Emphysema in the Asthmatic Patient.—The authors report 15 cases among 2000 asthmatic adults, with the median age of the accident being 42 years.

A Factor of Mental Anorexia of Adolescence: Rejection of Material Needs as an Affirmation of "Pure Intellectualism."—Five illustrative cases are described of ambitious adolescent girl students from poor families who appeared to reject their parents social and spiritual background by means of severe anorexia. These girls were all of superior intelligence, but their feelings toward their parents were dominated by ambivalence, arising from recognition of the parental sacrifices for their education and disdain for the parents lack of culture.

Treatment of Asthma with Predisone.—Sixteen severe cases of asthma were treated, twelve of which were in status, several with cyanosis, and three with associated cardiac failure. Doses of 50 mg. per day using 5 mg. tablets orally in status, and 15 to 20 mg. per day in chronic asthma were effective. Prednisone appeared to have three to four times the anti-inflammatory effect of ACTH and cortisone, with less sodium-retaining

effect. Remissions were no longer after prednisone therapy than with other steroids. Advantages were the smaller doses and lack of sodium-retaining effect in asthmatics with associated congestive failure.

Psychasthenic Child.—The author argues that the concept of psychasthenia as described by Janet in 1903 should not be abandoned in pediatric practice. Children who have vague physical complaints in spite of frequently normal physical status, coupled with a strong physic component of fatigue, confusion, lack of ambition, etc., in spite of normal intelligence can still be profitably considered and handled with the concepts of Janet in mind. The child with "psychasthenia" may be considered to have a curable condition, but also one which may be the beginning of more serious difficulties.

Nervous Manifestation of Infectious Mononucleosis.—In an excellent review article with illustrative case reports, the author described four principal forms of nervous involvement: (1) Meningeal forms of the disease in which there may be normal spinal fluid without clinical manifestations, or conversely clinical meningitis with normal spinal fluid. The Paul Bunnel test is positive in the blood and weakly positive in the spinal fluid. (2) The encephalitic form, including meningoencephalitis, meningoencephalomyelitis, or pure encephalitis; (3) The peripheral form of nervous involvement with paralysis of one or more cranial nerves, a Guillain-Barre-like syndrome, and (4) Ocular forms of nervous involvement, including optic neuritis, papilledema, or iridocyclitis. The author also stresses the value of the EEG in following the patients with infectious mononucleosis who have encephalitic involvement.

Extra-Dural Hematomas of the Cerebellar Fossa.—On the basis of 6 personal cases observed at the Neuro-Surgical Clinic of "Hopital de la Pitie" and 46 further cases from the literature, the authors present a collective study of the extradural hematomas of the posterior fossa. These assume four clinical appearances: superacute, acute, subacute, or chronic, latent forms. The first form, extremely serious, is oftenest beyond surgical possibilities. The second form, with a more favorable operative prognosis, shows often a fallacious symptomatology, identical to that of subtentorial hematomas. The subacute or chronic forms, which are clinically the most typical, show most usually such precise signs of posterior localization as justify by themselves an exploration of the cerebellar fossa.

Diagnosis is facilitated (1) by simple radiography of the cranium in frontosuboccipital direction which reveals in over 80% of cases a fracture line involving the posterior fossa; (2) by ventricular puncture which may often show in subacute forms a hydrocephalus due to blocking of the aqueduct; (3) by cerebral angiography involving up to the venous field. This angiography, when feasible, shows a conclusive feature: the detachment of the torcular Herophili.

Of the 46 cases in the literature, 41% were in children under 15 years, 33% between 15 and 30 years, and 26% between 30 and 70 years. They are generally single, but may be bilateral or associated with hematoma in other locations. One should chiefly attempt to detect this variety of traumatic hematoma as this is often overlooked and carries a more favorable operative prognosis than the extradural hematomas of the subtentorial floor, except for the subacute forms.

Nervous Manifestations of Infectious Mononucleosis (II).—Pathological examination of the brain has rarely been performed in this entity, since it is generally relatively benign. In four cases drawn from the literature perivascular infiltrations were noted in all, of the type associated with virus encephalitides. In discussing the etiology of the nervous manifestations, the question has been raised as to whether it is due to the virus itself or to an incidental encephalitis due to some other agent. Various forms of bacterial and viral encephalitis should be considered in differential diagnosis. BAL, ACTH, or artificial hibernation have been suggested in treatment but are of dubious value. The author stresses that infectious mononucleosis, which is generally benign, may be associated with severe and even fatal nervous involvement.

Utility of Heparin in the Treatment of Lipoid Nephrosis.—The authors report three cases of lipoid nephrosis in patients age 3, 38, and 56 years old in which heparin in doses of 50 mg. b. i. d. (I. V.) (adults) and 25-40 mg. b. i. d. (I. V.) (child) resulted

in a very successful diuresis. The authors emphasize that heparin was merely useful as a successful diuretic and had no influence on the basic disorder.

Paper Electrophoreses: Critical Review.—The authors tested a new chemical compound which is not merely a combination of PAS and INH but which constitutes a new antibiotic substance suitable for treatment of tuberculosis in daily doses of 0.1 gm. per kilogram of body weight. Fifty-eight cases were treated, forty-eight with pasiniazide alone and sixteen in combination with streptomycin (3 gm. per week). Half of the patients showed mild digestive disturbances within the first four to six days and only in seven cases did the drug have to be stopped because of intolerance in the first two weeks. All except one patient gained weight with an average of 2 to 3 kg., and there was great improvement in general physical status. The sedimentation rate decreased in 90%. Two out of five patients who were passing tubercle bacilli in the urine remained positive, and another patient who was negative at the start of treatment became positive during treatment. Twenty-one of the thirty-five patients with pyuria cleared during treatment. X-ray evidence of improvement was not very great. In reporting these results the authors emphasized that all patients treated were those who had been unsuccessfully treated previously with PAS, INH, and streptomycin.

Surgical Treatment of Pulmonary Stenosis Under Direct Vision.—Description of a new technique and presentation of the first case successfully operated on.

Kala-Azar and the Nervous System (with Description of Two Cases of Epilepsy Occurring Late in the Disease).—Neurological complications of leishmaniasis have been rarely reported. On the other hand, the treatment of kala-azar has been followed fairly frequently by neurologic complications. Glucantine (N-mentyl-glucamine antimoniate) has been reported to cause fatal hemorrhagic encephalitis. Neostibosan has caused paralysis and polyneuritis. The diamidine aromatic compounds, and especially stilbamidine, have caused epilepsy and other nervous manifestations. In 41 out of 45 cases treated in one series, neurologic complications occurred, often several months after the end of treatment, and involved especially the fifth, seventh, and ninth cranial nerves. Pentamidine has only rarely caused complications, and the salts (lomidine NB800) have caused chiefly GI and cardiovascular defects. The authors report two cases of convulsive disorders in children age 18 months and 2 years who had been successively treated 8 months and one year previously for kala-azar with glucantine and lomidine.

Treatment of Childhood Schizophrenia.—It is hard to judge the effectiveness of treatments in schizophrenia, since the late cases are unresponsive to any sort of therapy and those which are curable in early stages are open to the question of actual diagnosis. These difficulties are aggravated in the case of childhood schizophrenia as the onset of the disorder is more difficult to detect and the diagnosis is frequently not made till the condition is far advanced. The commonest form is that of the progressive dementia of Morel, in which there is a progressive weakening of the intellect, with very few remissions. The hebephrenic form of adolescence is occasionally seen in older children and shows less tendency to remission than in adolescence. The paranoid form which is seen in adults is practically never seen in children. The prognosis on treated childhood schizophrenia, with fewer remissions and more rapid and complete mental deterioration, is more gloomy than that of adolescence or adult schizophrenia. Treatment with insulin shock is not more dangerous in children than in adults but is apt to be more effective after the age of 16. Electroshock therapy is effective for the eventual anxiety component. Psychosurgery (lobotomy or topectomy) may be of value against aggressive tendencies. The authors are dubious about psychotherapy, which is currently popular in American practice, based on the theory that schizophrenia results from defective parental and especially maternal love in the first months of life. The authors believe that psychotherapy can only be useful as a complimentary treatment of the child and his environment during remission. Ergotherapy uses drawing and activity games to make contact with the child. None of the methods of therapy in current use appear very effective, but of all these the authors prefer the use of insulin shock when children are at least 9 years old. They do not believe one can speak of cured schizophrenics even in favorable cases.

First Experimental Results in France of Cardiac Surgery with the Oxygen-Pump System of Lillehei-DeWall.—After extensive work with dogs the authors used the oxygenator-pump system of Lillehei to successfully repair an interventricular septal defect in a 4-year-old child. This artificial heart-lung system now permits open cardiac surgery up to and even longer than 30 minutes in duration. They point out that simple clamping of the vena cava permitted cardiac intervention of only two minutes, subject to cerebral anoxia; hypothermia permits intracardiac surgery lasting 10 minutes and is limited by the grave risk of ventricular fibrillation. The artificial heart-lung system poses great problems of hemolysis, temperature, and hemoglobin control as well as oxygenation, but is a highly encouraging technique.

Treatment of Human Tuberculosis with Cycloserine.—The authors report the results in 80 tuberculosis patients treated with cycloserine for the last 10 months. There was 60% to 75% improvement among the patients who for the most part had severe cavitary disease no longer responsive to the usual antibiotics. Cycloserine was given in daily doses of 250 mg. b. i. d. initially, increasing to 250 mg. five times daily. There was no evidence of bacterial resistance developing to this medication. Cycloserine combined with INH was very effective in a large number of cases and allowed the dosage of cycloserine to be lowered and better tolerated. Toxic effects of cycloserine were phychomotor disorders in 12 cases, 5 of whom had convulsions. These toxic symptoms may occur suddenly without prodrome, but oftener were preceded by minimal CNS signs such as lassitude, slight visual disturbances, and feeling of unreality, which are good indications for discontinuing treatment for several days.

Preliminary Note on the Oral Treatment of Diabetes with D 860 (N-[Sulfonyl-*p*-Methylbenzene] N-Butyl Urea).—D 860 is the latest of the hypoglycemia-inducing compounds which are effective by mouth in diabetic subjects. Since January, 1956, at the Medical Clinic of the Hospital Cochin, in Paris, it has been studied in 27 patients. The drug has no antibacterial action, is well tolerated, and caused no toxic manifestations. It appeared suitable in subjects over 40 years of age with mild diabetes uncontrolled by diet alone. The average dose was 2 gm. daily. It was suggested that D 860 might be used in conjunction with insulin in younger patients, making it possible to reduce the insulin dosage. Long-term follow-up will be necessary to determine whether prolonged treatment is harmless.

Radiology, Syracuse, N. Y.

66, No. 6, 1956

* The Roentgen Findings in Primary Hepatoma in Infants and Children: An Analysis of Eleven Cases. Alexander R. Margulis, Charles M. Nice Jr., and Leo G. Rigler.—p. 809.

The Roentgen Findings in Primary Hepatoma in Infants and Children: An Analysis of Eleven Cases.—Although of low incidence, hepatoma is one of the commonest neoplasms of the liver in infancy and early childhood. The roentgen findings which aid greatly in making the diagnosis depend upon the location of the tumor in the liver.

When the right lobe (five cases) was involved, there was a large mass in the right upper abdomen inseparable from the liver. The lower border was wavy and frequently extended beyond the midline. The hepatic flexure of the colon was depressed, the transverse colon usually displaced anteriorly and downward, and the stomach usually displaced somewhat to the left and anteriorly oftener than posteriorly. There was no displacement of the duodenojejunal juncture, but the right kidney occasionally was displaced downward, medially and posteriorly.

When the tumor was in the left lobe (three cases), there was a large centrally located upper mass, extending to the left, inseparable from the liver. The splenic flexure of the colon sometimes was depressed. The transverse colon frequently was displaced anteriorly down or up with the peritoneal attachment remaining posterior. The stomach was markedly displaced to the left and sometimes displaced anteriorly or posteriorly. Here the second portion of the duodenum served as an anchoring point. The duodenojejunal juncture was displaced downward. The left kidney occupied a normal position or was depressed and pushed back.

When the entire liver (three cases) was involved, the x-ray findings were a combination of those encountered in the individual lobes.

In the majority of cases of primary carcinoma of this group, the diagnosis was made by simple gastrointestinal examinations and urographic studies with the aid of lateral views.

The most helpful clinical sign was the presence of a growing upper abdominal mass and anemia. Seven of this group were girls. The age varied from 4 days to 9 years, seven being less than 14 months old. In four the abdominal mass was discovered in routine physical examinations. In the others symptoms consisted of tiredness, weakness, and some form of abdominal pain. Two had mild jaundice; ten were anemic.

The differential diagnosis of primary carcinomas of the liver include sarcoma, hemangioendotheliosarcoma, Hodgkin's, liver cysts, Wilms' tumor, and Neuroblastoma with liver metastasis. Wilms' Tumor and Neuroblastoma can be demonstrated to be retroperitoneal. Superficial nodes are commonly present in Hodgkin's. Cysts have a tendency to be sharply demarcated and have the smooth rounded margin in contrast to the wavy outline of a hepatoma. The rarer sarcoma and hemangioendotheliosarcoma cannot be deferentiated by the x-ray method.

Zeitschrift für Kinderheilkunde, Berlin

78, No. 2, 1956

Chondro-Ectodermal Dysplasia (Ellis-van Creveld. H. Weyers.—p. 111.

The Symptomatology of Pyogenous Recidivous Parotitis (Review and 5 Case Reports). P. Krepler.—p. 130.

Daily Fluctuations of Electrical Skin Resistance in 11 Year Old Children. J. Rutenfranz, T. Hullbruegge, and W. Niggeschmidt.—p. 144.

Electro-Encephalographic Changes in Oxycephalus. H. Fritzsche and I. Fritzsche.—p. 158.

Studies on Experimentally Produced Pneumocytosis in Rats and Its Significance for the Understanding of Interstitial Pneumonia in Prematures. R. Weller.—p. 166.

Studies of the Phenylalanine and Tyrosine Metabolism in a Child with Phenylpyruvic Oligophrenia. I. Hamann.—p. 177.

The Influence of Cerebral Disturbances upon the Carbohydrate Metabolism (Hypoglycemia and Diabetes Mellitus). K. Mueller.—p. 185.

* Temporary Arterio-Mesenterial Obstruction of the Intestines: A Cause for Unexplained Abdominal Pains. W. Schermuly.—p. 197.

Catabolism of Proteins and Fats in Homogenized and Non-Homogenized Cow's Milk. C. A. Sager.—p. 210.

Susceptibility to Convulsions and Age: Studies of the Convulsive Threshold to Cardiazol in Rabbits. W. Theopold and E. Færster.—p. 219.

Dittrich, J. K.: Contributions to the Pathogenesis of Acute Nutritional Disturbances: III. Water Content of the Chyme in the Different Sections of the Gastrointestinal Tract. J. K. Dittrich.—p. 232.

78, No. 3, 1956

Studies on Growth in Weight in Infancy (Contribution to the Problem of Accelerated Growth). W. Theopold and H. Zwilling.—p. 243.

Amino Acid Intake and Damage to Kidney Tubuli. U. Stave and E. Schlaak.

I. Amino-Aciduria in Rabbits Following the Feeding of Cystine.—p. 261.

II. Function of Kidney Tubuli in Rabbits Following the Feeding of Cystine.—p. 275.

Macromolecules of Globulin Occurring as a Symptom of Congenital Lues. F. Koch, K. Schlageter, and G. Schwick.—p. 283.

* Chronic Arthritis of the Cervical Spine in Childhood. M. Senger.—p. 301.

Dysostosis Enchondralis Epiphysaria Occurring with Bilateral Aseptic Femoral Head Necrosis: Contribution to the Pathogenesis of Perthes' Disease. F. Locher.—p. 311.

The Provocation of Colonic Movements Seen Under X-Ray by Contact Laxatives. W. Schermuly.—p. 319.

Blister Formation in Epidermolysis Bullosa. W. Plenert.—p. 329.

Pituitary Dwarfism and Thyrotropic Hormone Insufficiency. G. A. Harnack and J. R. Bierich.—p. 341.

Temporary Arterio-Mesenterial Obstruction of the Intestines: A Cause for Unexplained Abdominal Pains.—Among 122 cases investigated for unexplained abdominal pains the author found 10 as being caused by partial duodenal stenosis due to intestinal and mesenterial developmental defects.

The stenosis was diagnosed roentgenographically, was only partial and never a threat to the patient's life. It could be relieved by placing the patient in prone position. It was caused probably by compression of the duodenum by the mesenterial blood

vessels and torsion of the blood vessels due to incomplete developmental rotation an attachment of the mesenterium. A mobile cecum was diagnosed in these cases. The roentgenographic picture shows an obstruction running parallel to the body axis with dilatation of the proximal part of the duodenum. The cecum is either displaced or can be demonstrated to be mobile. Enlarged deep mesenteric lymph nodes are the most important differential diagnostic consideration.

The author describes two typical cases (13- and 11-year-old boys), and a third case, a 12-year-old child in whom the diagnosis of a duodenal stenosis of moderate degree was made and a mobile cecum proved. On operation both were confirmed, but the reason for the stenosis was found to be enlarged, clumped lymph nodes.

The literature on this subject is reviewed and 65 references are cited.

Chronic Arthritis of the Cervical Spine in Childhood.—The case of an 8-year-old boy is described who complained of pains in head and extremities for one year and presently of pains in the neck and tenderness over the lower cervical spine. A history of frequent attacks of tonsillitis and rheumatic disease in the maternal branch of his family was elicited. Roentgenograms showed changes in the intervertebral joints between C-2 and C-3.

Cervical arthritis in acute polyarthritis is very rare (two references cited) but has been described in textbooks in chronic polyarthritis. The author reviews the literature on this subject and states that complete ankylosis has been described, presenting a picture resembling the Klippel-Feil syndrome of congenitally absent segmentation of the cervical spine.

The author describes the clinical picture of "chronic polyarthritis," a term used in the German literature and considered more descriptive than the term of "rheumatoid arthritis" used in America, since it indicates the chronicity as well as affection of more than one joint. The differential diagnosis—although the primary complaints may resemble those of meningitis—should present no difficulties on the basis of roentgenograms, since osteomyelitis as well as tuberculosis occur almost exclusively in the vertebral body or intervertebral disc.

News and Comment

ANNOUNCEMENTS

Course in Pediatric Oncology.—The Pediatric Department of the Memorial Center for Cancer and Allied Diseases announces that the annual comprehensive three-day course in pediatric oncology for pediatricians, general practitioners, health officers will be held April 24, 25, and 26, 1957.

Current developments and established methods in diagnosis, differential diagnosis, and management of benign and malignant tumors, Hodgkin's disease, leukemia, and reticuloendothelioses in childhood are included.

Content of course: Ward rounds, seminars, demonstrations, examinations of children in pediatric, surgical, chemotherapy, radiotherapy clinics.

Faculty: Twenty members of the Attending Staffs of Memorial Hospital and Sloan-Kettering Institute for Cancer Research.

Class limited to 15 physicians. Fee: $35.00.

For information address Director, Pediatric Service, Memorial Center, 444 East 68th Street, New York.

National Foundation for Infantile Paralysis Postdoctoral Fellowships.—March 1 is the deadline this calendar year for submitting applications to the National Foundation for Infantile Paralysis for postdoctoral fellowships. Applications submitted before that date will be considered by the appropriate National Foundation Fellowship Committee in May.

Postdoctoral fellowships are available (a) in rehabilitation, either the concept and basic techniques applied to specialized fields in medicine or for preparation in the specialty of physical medicine and rehabilitation; (b) in psychiatry; (c) in orthopedics; (d) in the management of poliomyelitis; (e) in preventive medicine; (f) for postdoctoral training in research and/or academic medicine.

In addition to a monthly stipend which varies from $3600 to $6000 annually according to the individual needs and marital status of the applicant, the National Foundation arranges for compensation to the institution according to the program undertaken. For a full academic program, tuition and fees are paid; for other programs, a sum not to exceed $1250.00 per year including tuition is paid. Partial fellowships are available for qualified veterans to supplement G. I. educational benefits.

The next deadline for applications will be September 1 for consideration in May.

For further information write Division of Professional Education, National Foundation for Infantile Paralysis, 120 Broadway, New York 5, N. Y. (After March 1, 1957, write to our new address 301 East 42nd Street, New York, N. Y.)

American Orthopsychiatric Association Meeting.—More than 5000 mental health specialists are expected to attend the thirty-fourth annual meeting of the American Orthopsychiatric Association at the Hotel Sherman, Chicago, March 7, 8, and 9, 1957.

They will include psychiatrists, psychologists, social workers, educators, public health workers, and clinic and institutional administrators from all parts of the United States and Canada. Arrangements are being made for attendance by nonmembers of the Association, according to Dr. Marion F. Langer, executive secretary of the Association.

The Association is a membership organization of the three major disciplines concerned with treatment of human behavior: psychiatry, psychology, and social work. Its members also include educators, anthropologists, sociologists, and pediatricians.

The American Academy of Child Psychiatry and the American Association of Psychiatric Clinics for Children will hold their annual meetings simultaneously.

The 60 papers to be presented will deal with theoretical and practical aspects of schools and mental health, inpatient and outpatient psychiatric treatment of children, adolescence and juvenile delinquency, psychiatric clinic management, adult psychotherapy, current social

changes and their mental health implications, and international and intercultural factors of mental health. Also scheduled are 33 workshop sessions, mental health film showings, and technical and commercial exhibits related to mental health.

Postgraduate Courses in Pediatrics.—Two postgraduate courses in pediatrics are being offered by the Department of Pediatrics, Harvard Medical School, at Massachusetts General Hospital in June, 1957.

1. Pediatrics 3—June 3 to 14, inclusive, 1957; daily 9:15 a.m. to 4:30 p.m. This course provides a general review with emphasis on recent advance and therapy. The first seven days are devoted to pediatric medical, surgical, orthopedic, cardiac, allergic, dermatologic, psychiatric, eye, ear, and x-ray problems. The last four days concentrate on disorders of growth and development, common endocrine problems, and the metabolic aspects of infant feeding, parenteral fluid therapy, and management of nephritic and diabetic patients.

2. Pediatric Metabolism and Endocrinology—June 11 to 14, inclusive, 1957; daily 9:15 a.m. to 4:30 p.m. This course is the same as the last four days of Pediatrics 3 as described above, but may be taken separately.

Those interested should write Courses for Graduates, Harvard Medical School, 25 Shattuck Street, Boston.

Fellowships in Child Health and Preventive Medicine.—The Johns Hopkins University School of Hygiene and Public Health is offering the following Fellowships in Child Health and Preventive Medicine: One-Year Fellowships—stipends $3800 to $5000; Two-Year Fellowships—stipends $5000 to $7000.

These fellowships are designed for persons who wish to prepare themselves for a career in public health, for an academic post in preventive medicine, or to return to academic pediatrics with a background in epidemiology, biostatistics, and public health.

Applicants accepted for a one-year fellowship will take courses leading to the Master of Public Health degree with a major in Maternal and Child Health and will serve as pediatricians in our Family Health Study for about three months.

Applicants accepted for the two-year fellowship will hold a faculty appointment and will participate in our teaching of medical students. They will take courses for the Master of Public Health degree over a two-year period.

The children in our Family Health Study are given complete medical care in health and in illness by a group of pediatricians, public health nurses, social workers, and psychologists. These families are selected for long time participation in the Study and serve as the basis for our teaching and research.

Applicants must have completed two years of pediatric training and qualify for concurrent appointment in the Department of Pediatrics.

Refresher Course in Pediatrics.—A refresher course in pediatrics will be conducted at St. Christopher's Hospital for Children, Philadelphia, by the pediatric department of Temple University School of Medicine on May 22 to 25, 1957. Each half-day session will be devoted to a single phase of pediatric medicine. For information regarding enrollment, registration fee, etc., write to Dr. John B. Bartram, St. Christopher's Hospital for Children, 2600 N. Lawrence Street, Philadelphia 33, Pa.

Residencies in Pediatric Pathology.—Residency positions are available in pediatric pathology at The Children's Hospital of Philadelphia for the year 1957-1958. The department of pathology is closely affiliated with the School of Medicine and Graduate School of Medicine, University of Pennsylvania. The residency program provides for experience in anatomical pathology and research. The research laboratories are engaged in a variety of problems dealing with basic science and clinical investigations. Residents are also encouraged to participate in clinical conferences, ward rounds, and clinics.

A limited number of fellowships are available for research in pediatric pathology. Candidates should have completed at least one year of residency training in pediatrics or one year in research.

Address all inquiries to Bernard M. Wagner, M.D., Department of Pathology, The Children's Hospital of Philadelphia, 1740 Bainbridge Street, Philadelphia 46, Pa.

SOCIETY NEWS

American Academy for Cerebral Palsy Officers.—The American Academy for Cerebral Palsy held its 10th Annual Meeting in Chicago (Headquarters at Congress Hotel) Nov. 17, 18, and 19, 1956.

The officers for the forthcoming year are Dr. Nicholson J. Eastman, President, Johns Hopkins Hospital, Baltimore; Dr. William T. Green, President-Elect, 300 Longwood Avenue, Boston; Dr. Raymond R. Rembolt, Secretary-Treasurer, The Iowa Hospital-School, State University of Iowa, Iowa City.

The 1957 meeting will be held in New Orleans, Nov. 25, 26, and 27, at the Roosevelt Hotel.

Intermountain Pediatric Society Convention.—The Intermountain Pediatric Society will hold its annual clinical convention at the Hotel Riviera, Las Vegas, Nev., March 18 and 19, 1957. Guest speakers will include Dr. Sidney Gellis, Boston; Dr. James Wilson, Ann Arbor, Mich.; Dr. John A. Anderson, Minneapolis. The meeting is open to all physicians. For further information write Intermountain Pediatric Society, 2000 South 1300 East, Salt Lake City 5, Utah.

GENERAL NEWS

Specialists Certified by the American Board of Pediatrics, Inc.—The following physicians were certified as specialists by the American Board of Pediatrics, Inc., in St. Louis, Dec. 7-9, 1956.

Aaronson, L. Clarke, Salt Lake City, Utah.
Adam, Doris, J. D., Galveston, Texas.
Anast, Constantine Spiro, Columbia, Mo.
Babich, John Marion, Sacramento, Calif.
Ball, James A., Dallas, Texas.
Barron, William Paul, Harrison, Ark.
Binney, Charles II, Harlingen, Texas.
Boelsche, Arr Nell, Galveston, Texas.
Brennan, Patricia Anne, Brentwood, Mo.
Buddrus, David James, Kansas City, Mo.
Chase, Ralph, San Angelo, Texas.
Cohan, Stuart Kenneth, Bellaire, Texas.
Comstock, Howard Clement, Lansing, Mich.
Conkling, William Scott, Navasota, Texas.
Creasman, Richard W., Phoenix, Ariz.
Crellin, Paul Ronald, Billings, Mont.
Endres, Robert K., Tulsa, Okla.
Haggard, Mary Ellen, Galveston, Texas.
Hardie, Robert Huff, Houston, Texas.
Harris, Mack J., San Diego, Calif.
Harris, Thomas Sharit, Laramie, Wyo.
Hauptmann, William Louis, Royal Oak, Mich.
Heiner, Douglas Cragun, Little Rock, Ark.
Heitman, Henry Schrader, Baton Rouge, La.
James, David Hamilton, Jr., Memphis, Tenn.
Kauffman, Avner, Chicago.
Kelly, Vermelle C., St. Louis.
La Forte, Peter, Brooklyn.
Laughmiller, Roy William, Jr., Maryville, Tenn.
Maisel, Jerome Edmund, Hewlett, N. Y.
Méndez Polo, Ceferino A., Santurce, Puerto Rico.
Moore, William Finley, Jr., Honolulu, Hawaii.
Nash, Homer Erwin, Jr., St. Louis.
Pavy, Robert Louis, Lafayette, La.
Peden, Virginia H., University City, Mo.
Petersen, Don C., Long Beach, Calif.
Pharo, Milam Bernard, Dallas, Texas.
Scheurich, Mary Barbara, LaCrosse, Wis.
Schloesser, Patricia T., Topeka, Kan.
Shepherd, Edwin Collier, Savannah, Ga.
Sherrod, Henry L., Jr., Birmingham, Ala.
Smith, Dorothy I., Omaha.
Sparling, David L., Mt. Edgecumbe, Alaska.
Stone, Benjamin Jennings, Lansing, Mich.
Townsend, Thomas Edward, Pine Bluff, Ark.
Van Adelsberg, Stephan B., Los Angeles.
Wishingrad, Lester, Chicago.
Wiggins, Casper E., Greenwood, S. C.

Special Foreign Certificates

Shein, Max, Mexico D.F.
Sinclair, Seeta, Grand Rapids, Mich.
Stickler, Gunnar B., Obb., Germany.

The following listed physician was certified at New York, Oct. 13, 1956, and will receive a Special Foreign Certificate: Lin, Hilda Feng-Kai, New York.

Books

BOOKS RECEIVED

Kinderærztliche Notfallfibel. By B. de Rudder. Price, $3.95. Pp. 178, with 22 illustrations. Georg Thieme Verlag, Intercontinental Medical Book Corporation, New York 16, Aug. 16, 1956.

Preventive Medicine and Public Health. Ed. 8. Edited by Kenneth F. Maxcy. Price not given. Pp. 1465, with numerous illustrations. Appleton-Century-Crofts, Inc., 35 West 32nd Street, New York 1, 1956.

Disease in Infancy and Childhood. By Richard W. B. Ellis. Price, not given. Pp. 710, with 304 illustrations. Williams & Wilkins Company, Baltimore, 1956.

Masked Epilepsy. By Hugh R. E. Wallis. Price, $2.50. Pp. 51. Williams & Wilkins Company, Baltimore 2, 1956.

Environment and the Deaf Child. By Steven Getz. Price, $3.75. Pp. 173, with 20 Tables. Charles C Thomas, Publisher, 301-327 East Lawrence Ave., Springfield, Ill., August, 1956.

Pre and Postoperative Care in the Pediatric Surgical Patient. By William B. Kiesewetter. Price, $7. Pp. 347, with 49 illustrations, Year Book Publishers, Inc., 200 East Illinois Street, Chicago, 1956.

The Person Behind the Disease. By Julius Bauer. Price, $3.50. Pp. 136, with 5 illustrations. Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, October, 1956.

Sick Children. Ed. 7. By Donald Paterson and Reginald Lightwood. Price, $8.75 (North American market only). Pp. 593, with 82 illustrations. J. B. Lippincott Company, East Washington Square, Philadelphia 5, October, 1956.

Diseases of the Heart. Ed. 2. By Charles K. Friedberg. Price, $18. Pp. 1161, with 157 illustrations. W. B. Saunders Company, West Washington Square, Philadelphia 5, 1956.

Practical Pediatric Dermatology. By Morris Leider. Price, $10.50. Pp. 433, with 115 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, September, 1956.

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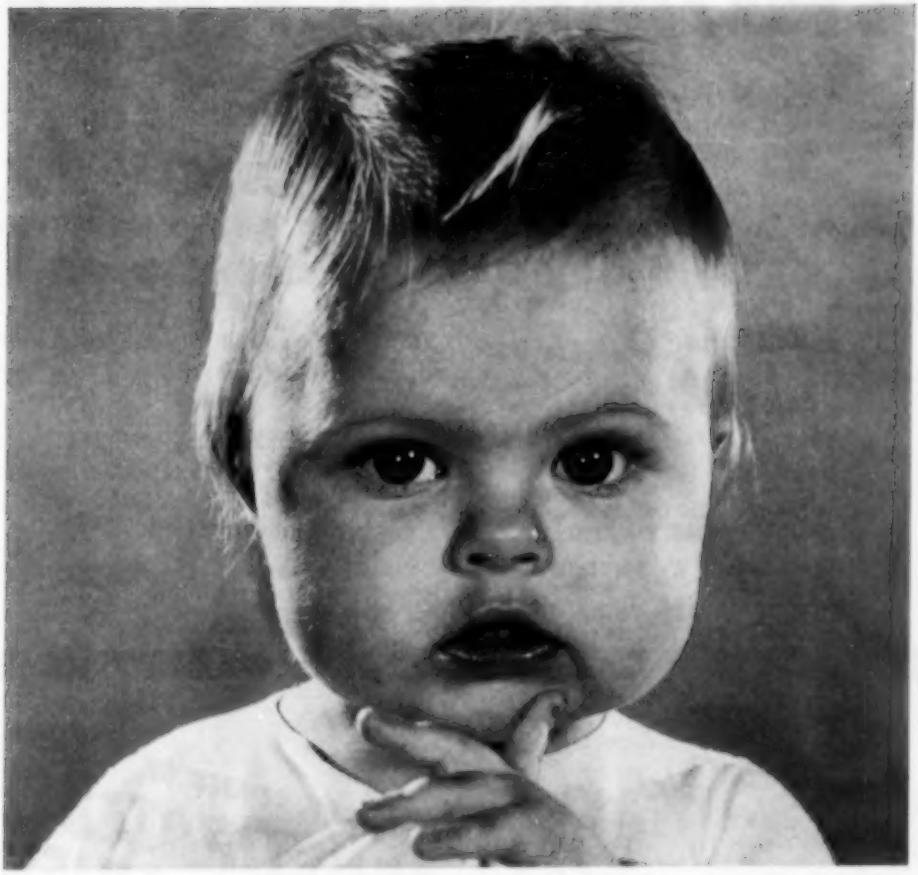

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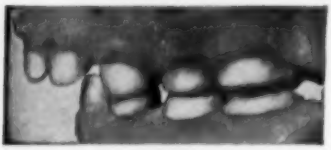

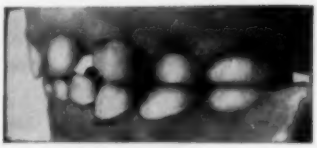

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On the Protein Quality of the Oatmeal Serving

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Feeding tests with small animals and human subjects indicate the amino acids of rolled oats to be readily available for absorption and utilization because of the high digestibility of oat protein.[3, 4, 5] The high nutritional value of the rolled oats-and-milk combination was proved many years ago in human feeding experiments in which the protein value was studied in terms of maintaining nitrogen equilibrium.[6] The excellent quality of the combination of proteins in the standard serving of oatmeal and milk is also evident in results of growth tests with weanling rats.[7]

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1. Watt, B.K., and Merrill, A.L.: Composition of Foods—Raw, Processed, Prepared, Washington, D.C., United States Department of Agriculture, Agricultural Handbook No. 8, 1950.
2. Sure, B.: Nutritional Values of Proteins in Various Cereal Breakfast Foods, Food Res. *16*:161 (Mar.-Apr.) 1951.
3. Murlin, J.R.; Nasset, E.S., and Marsh, M.E.: The Egg-Replacement Value of the Proteins of Cereal Breakfast Foods, With a Consideration of Heat Injury, J. Nutrition *16*:249 (Sept.) 1938.
4. Mitchell, H.H., and Block, R.J.: Some Relationships Between the Amino Acid Contents of Proteins and Their Nutritive Values for the Growing Rat, J. Biol. Chem. *163*:599 (June) 1946.
5. Clark, L.C.; Ryer, H., and Murlin, J.R.: Relative to Egg Biological Values and Replacement Values of Some Cereal Proteins in Human Subjects, J. Nutrition *38*:405 (Aug.) 1949.
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7. Quaker Oats Company Research Laboratories Project Report.

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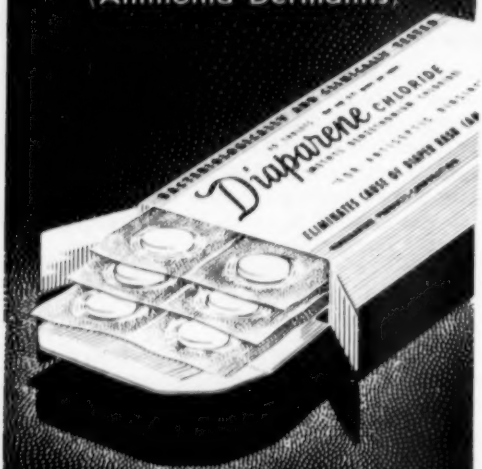

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The Contribution of *Enriched Bread* to Childhood Nutrition

"Children reared on nutritionally adequate diets have many advantages over those reared on poor diets. These advantages include: better growth and development; greater strength and vigor; and more evidence of good general nutrition."[1] The nutritional status of millions of American school children has been enhanced significantly by enriched bread during the past fifteen years, and for these reasons:

Enriched bread contains thiamine, riboflavin, niacin, calcium, iron, and protein. All have made important contributions to the reduction of deficiency diseases traced to the lack of these nutrients. Many authorities cite the virtual elimination of deficiency diseases in recent years as impressive evidence of the role enriched bread has played.[2]

Enriched bread, containing added nonfat dry milk, provides a highly nutritive protein combination derived from three sources —flour, milk and yeast—with milk and yeast proteins supplementing the flour protein. These proteins not only contribute to the maintenance and repair of children's tissues, but also to good growth.

Dental authorities agree that a good diet is an important factor in dental health. The complex carbohydrates present in bread—in contrast to the action of simple carbohydrates—do not readily diffuse into dental plaques and therefore are of low cariogenic activity.[3]

These are some of the reasons why the role of enriched bread, in improving the health of millions of American school children, has been referred to as one of the most important advancements in public health measures since compulsory pasteurization of milk.

1. Martin, E.A.: Roberts' Nutrition Work with Children, Chicago, University of Chicago Press, 1954, p. 53.
2. Sebrell, W.H.: Developing Modern Nutrition Programs, Public Health Reports, United States Department of Health, Education and Welfare 69:277 (Mar.) 1954.
3. Joint Report of the Council on Dental Health and the Council on Dental Therapeutics of the American Dental Association: Sugar and Dental Caries: The Effect on the Teeth of Sweetened Beverages and Other Sugar-Containing Substances, J. Am. Dent. A. 47:387 (Oct.) 1953.

AMERICAN BAKERS ASSOCIATION

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The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

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Designed especially for pediatric use, Varamel is unique in its field and should not be confused with ordinary evaporated milks.

FIRST—Varamel is made exclusively from Grade A Milk*, thus assuring a high quality, clean milk from the source of supply to the infant.

SECOND—Varamel is fortified with sufficient pure synthetic vitamins to provide the daily recommended allowance of all known essential vitamins.

THIRD—The butter fat is replaced by vegetable and animal fats which are particularly well-tolerated and utilized by the infant.

FOURTH—Iron is added to supply 7.5 milligrams per quart of formula.

FIFTH—Varamel contains only the sugar from the milk used, so the physician can add the necessary amount of carbohydrate to meet the nutritional needs of the infant.

Approximate Analysis

Protein	4.9%	Calcium	0.19
Carbohydrate	8.3	Phosphorus	0.15
Fat	5.8	Iron	0.0016
Ash	1.2	Moisture	79.8

Calories per fl. oz., 32

*Made from Grade A Milk (U. S. Public Health Service Milk Code)

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